





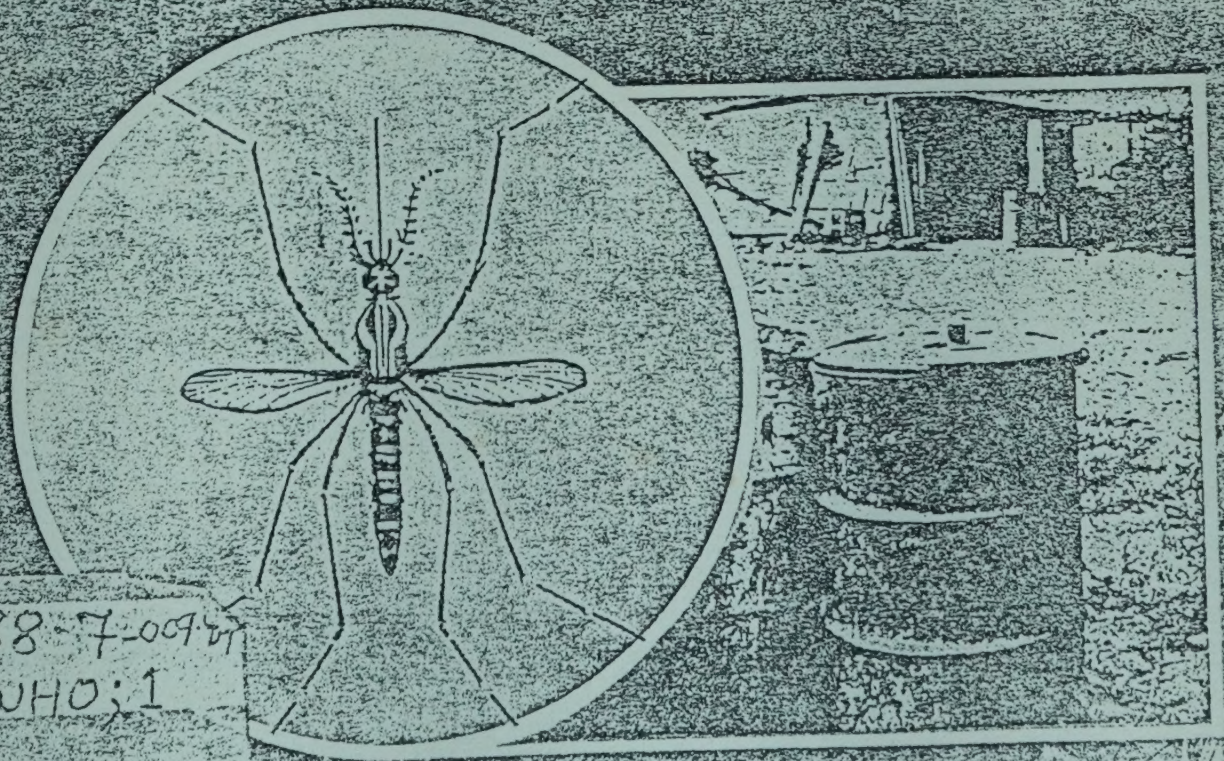
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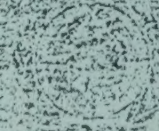
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# Dengue haemorrhagic fever:

diagnosis,  
treatment and  
control



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World Health Organization, Geneva



1942-1943

REPORT  
ON THE  
PROGRESS OF  
THE  
RESEARCH  
DURING THE  
YEAR 1942-1943





# NATIONAL INSTITUTE OF VIROLOGY

BANGALORE UNIT

VICTORIA HOSPITAL

BANGALORE-560 002

The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 165 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries; promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases including tuberculosis and leprosy; having achieved the eradication of smallpox, promoting mass immunization against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

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FROM THE FIRST SETTLEMENT  
TO THE PRESENT TIME  
IN TWO VOLUMES  
BY NATHANIEL BENTLEY  
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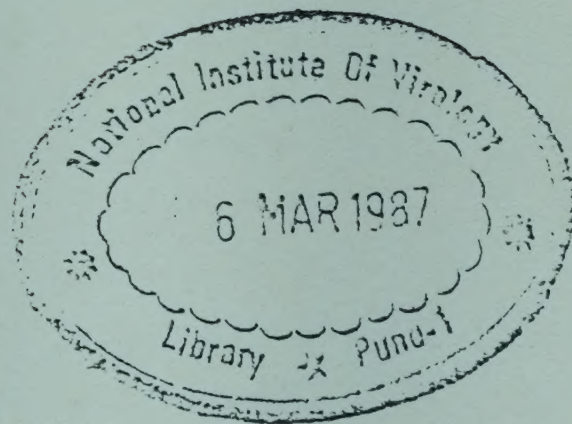
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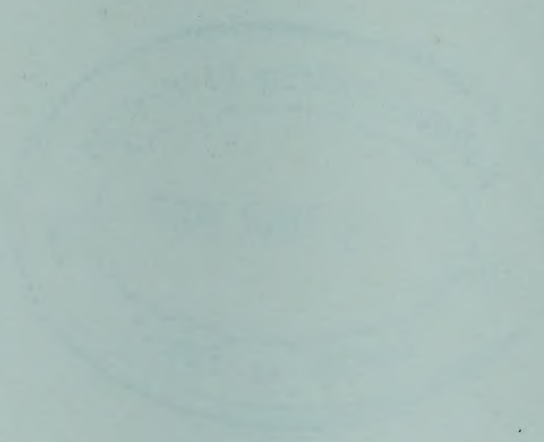




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treatment and  
control



WORLD HEALTH ORGANIZATION  
Geneva, 1986







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# Contents

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## Preface

1. General considerations . . . . .	1
Spreading outbreaks in the South-East Asia and Western Pacific Regions of WHO . . . . .	1
Outbreak of dengue haemorrhagic fever/dengue shock syndrome in Cuba, 1981 . . . . .	2
Other areas at risk . . . . .	2
Characteristics of outbreaks . . . . .	3
Transmission chain of dengue . . . . .	4
Pathology . . . . .	5
Pathogenesis of dengue haemorrhagic fever/dengue shock syndrome . . . . .	6
2. Clinical diagnosis . . . . .	7
Dengue fever . . . . .	7
Dengue haemorrhagic fever . . . . .	8
Dengue infections with central nervous system manifestations . . . . .	11
Criteria for clinical diagnosis of dengue haemorrhagic fever/dengue shock syndrome . . . . .	11
Case definition . . . . .	12
Grading the severity of dengue haemorrhagic fever . .	13
Differential diagnosis of dengue haemorrhagic fever/dengue shock syndrome . . . . .	14
Record sheet . . . . .	14
3. Treatment . . . . .	16
General considerations . . . . .	16
Dengue haemorrhagic fever without shock . . . . .	17
Dengue shock syndrome . . . . .	19
Outpatient and inpatient flow charts . . . . .	22
4. Laboratory diagnosis . . . . .	23
Collection of specimens . . . . .	23







Isolation of virus . . . . .	25
Serological tests . . . . .	26
5. Vector surveillance and control . . . . .	30
Surveillance . . . . .	30
Prevention and long-term control . . . . .	31
Emergency control . . . . .	32
Training . . . . .	32
6. Epidemiological surveillance, contingency plans, control, and prevention . . . . .	34
Factors increasing the risk of outbreaks of dengue haemorrhagic fever . . . . .	34
Surveillance of dengue haemorrhagic fever . . . . .	35
Development of epidemic contingency plans . . . . .	37
Control of outbreaks . . . . .	38
Prevention of dengue haemorrhagic fever . . . . .	40
Exchange of information . . . . .	40
7. Primary health care . . . . .	41
Recognition of dengue haemorrhagic fever cases . . . . .	41
Management of cases . . . . .	42
Collection of specimens for laboratory examination . . . . .	42
Mosquito control . . . . .	43
Bibliography . . . . .	44
Annex 1. List of participants—Technical Advisory Group on Dengue Haemorrhagic Fever/Dengue Shock Syndrome . . . . .	45
Annex 2. Dengue haemorrhagic fever record sheet . . . . .	47
Annex 3. Outpatient flow chart . . . . .	48
Annex 4. Hospital flow chart . . . . .	50
Annex 5. Arbovirus laboratory request form and reporting form . . . . .	52
Annex 6. WHO Collaborating Centres for Arbovirus Reference and Research . . . . .	54
Annex 7. Dengue haemorrhagic fever case-reporting form . . . . .	55
Annex 8. Check-list for management of dengue haemorrhagic fever outbreaks, surveillance, and reporting . . . . .	56







## Preface

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Following the extensive epidemics of dengue haemorrhagic fever that occurred in Burma, Indonesia, Thailand, and other countries in South-East Asia and the Western Pacific areas from 1972 onwards it was felt that a guide to the diagnosis, treatment, and control of dengue would be valuable for clinicians and other public health officers who were faced with an epidemic of this disease for the first time.

The first version of this guide was prepared by a technical advisory committee that met in Manila in 1974 and in Bangkok in 1975, and was issued in 1975 by the WHO South-East Asia and Western Pacific Regional Offices under the title "Technical guides for diagnosis, treatment, surveillance, prevention and control of dengue haemorrhagic fever".

A revised version, issued in 1980, was prepared by a technical advisory committee that met in Bangkok in 1978; the objective at that time was to present the diagnosis, treatment, and control of dengue haemorrhagic fever in the simplest possible way, in order to make the information accessible to primary health care services. At the same time it was desirable that the guide should contain all the technical data required by clinicians and public health officers. Few changes were made in the criteria for diagnosis and in the treatment recommended in the 1975 version.

The present edition was reviewed and discussed at a meeting of a technical advisory group in Kuala Lumpur in August 1983.<sup>1</sup> The group took into account the observations made during a recent outbreak in Cuba as well as experience gained in diagnosis, referral, treatment, and control in other countries, especially in the South-East Asia Region of WHO. This edition therefore reflects the latest knowledge of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) in all the WHO regions in which it occurs—the Americas, South-East Asia, and the Western Pacific. It is published in the hope that it will be of value to all health staff in those regions who are called upon to take care of cases of DHF/DSS, or who are concerned with routine surveillance and the control of outbreaks.

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<sup>1</sup> The participants are listed in Annex 1.







## 1. General considerations

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Dengue haemorrhagic fever (DHF) can be defined as an acute febrile illness caused by four serotypes of dengue virus and characterized clinically by a haemorrhagic diathesis and a tendency to develop a shock syndrome (dengue shock syndrome—DSS) that may be fatal. Thrombocytopenia with concurrent haemoconcentration is a constant finding.

### Spreading Outbreaks in the South-East Asia and Western Pacific Regions of WHO

The classical form of dengue fever (DF) is an acute febrile disease with headaches and joint and muscular pains. It has been known for more than a century in the tropical areas of the South-East Asia and Western Pacific Regions. However, the haemorrhagic form was first recognized as a new disease in the Philippines in 1953 (Philippine haemorrhagic fever) and in Thailand in 1958 (Thai haemorrhagic fever). These outbreaks caused some panic because of their novelty. The mystery concerning the causative agent was solved when dengue virus types 2, 3, and 4 were isolated in the Philippines in 1956 and dengue virus type 1 in Thailand in 1958. Between 1953 and 1964, DHF was described in India, Malaysia, the Philippines, Singapore, Thailand, and Viet Nam. After a period when DHF was endemo-epidemic in Thailand and the Philippines, there was a considerable increase in the number of reported dengue infections in the years 1971–78 in various countries of the South-East Asia and Western Pacific Regions. During the period 1975–78 in the first-named region a total of 17 251 hospitalizations (772 deaths) was reported in Burma, 21 818 hospitalizations (916 deaths) in Indonesia, and 71 312 hospitalizations (1676 deaths) in Thailand.

In the Western Pacific Region, reports of cases of DHF have been received since 1975 from Malaysia, the Philippines, and Singapore, since 1976 from Viet Nam, and since 1979 from countries in the South Pacific. In 1978, a big outbreak of DF occurred in the







southern part of China; this was caused by dengue virus type 4 and resulted in 22 122 cases and 14 deaths. In 1979-80, another big outbreak caused by dengue virus type 4 occurred in countries in the South Pacific and in Niue (population 3000), which resulted in 616 DF cases and 4 deaths. In 1980, 49 318 DF/DHF cases (462 deaths) were reported in Viet Nam. In 1982, an epidemic of DF/DHF with 3005 cases (35 deaths) was reported in Malaysia; dengue virus types 1, 2, and 3 were isolated.

An epidemic of DF caused by dengue virus type 3 occurred in the Solomon Islands in 1982; and in towns in north Queensland, Australia, a DF epidemic involving mainly dengue virus type 1, but also types 2 and 3, caused 455 confirmed cases in 1981-82.

Dengue haemorrhagic fever is now an increasing public health problem in most of the countries of the tropical areas of the South-East Asia and Western Pacific Regions. The disease is among the ten leading causes of hospitalization and death in children in at least eight tropical Asian countries.

#### **Outbreak of Dengue Haemorrhagic Fever/Dengue Shock Syndrome in Cuba, 1981**

In 1977, after more than 30 years' absence, dengue virus was introduced into Cuba. From serological surveys, it has been established that approximately 45% of the Cuban population was infected with dengue virus type 1 in the period 1977-80. In this outbreak the disease was predominantly mild. In 1981, dengue virus type 2 was introduced. A sharp outbreak resulted in 344 203 reported cases, the majority during a 3-month period. A total of 116 143 persons were hospitalized, an estimated 24 000 of these with DHF. Among approximately 10 000 shock cases, there were 158 deaths. Severe disease was seen predominantly in children under the age of 15 years. Among those hospitalized, a large proportion were adults; one-third of the fatalities were in adults. Although sporadic cases of DHF/DSS have been reported from several countries in the Region of the Americas over the past decade, the Cuban epidemic was the first outbreak of DHF/DSS to occur outside the South-East Asia and Western Pacific regions.

#### **Other Areas at Risk**

Other countries may also be considered to be at risk of DHF outbreaks. Dengue has been prevalent in tropical areas of Africa and the Americas and has appeared episodically in the temperate regions of North America, Africa, and the Mediterranean region of Europe. There are indications in the literature that cases similar to dengue





shock syndrome (DSS) occurred during some of the earlier outbreaks.

In India, serological and virological evidence has been found of dengue infections with the four serotypes, mainly in the south-east of the country, but no DHF outbreaks have been reported since those of 1963-65 in Calcutta. There is dengue activity in Sri Lanka but only sporadic DHF/DSS cases have been reported. A large number of islands in the Western Pacific Region were involved in a pandemic in 1974, caused by dengue virus type 1, while outbreaks caused by serotypes 2 and 3 had occurred previously. A somewhat similar development has occurred in the Caribbean islands, where a pandemic caused by dengue virus type 1 occurred in 1977 following outbreaks caused by serotypes 2 and 3.

### Characteristics of Outbreaks

Although the original outbreaks seemed to appear suddenly in the Philippines and in Thailand, retrospective studies indicate that they were probably preceded by a period when cases occurred but were not recognized. In Thailand, outbreaks occurred first in Bangkok, the pattern of epidemic activity at first having a two-year cycle; subsequently the cycles became irregular. DHF then became endemic in many large cities of Thailand and eventually spread gradually to smaller cities and towns during epidemics. A similar pattern has been observed in Indonesia and Burma.

A seasonal pattern of incidence, coinciding with the rainy season, has been observed in some countries.

In South-East Asia, DHF has been observed mainly in children. In Bangkok, where since 1968 there has been a trend towards reduced attack rates (constant hospital admissions despite an increasing population), the modal age of the hospitalized children has risen to 6-7 years, but throughout the rest of Thailand the modal age is still 4-6 years.

The attack rate of DHF is difficult to evaluate, as the number of dengue virus infections is usually unknown. A retrospective evaluation of the impact of DHF during an outbreak in Bangkok-Thonburi in May-November 1962 indicated that in a population of 870 000 children under 15 years of age there were an estimated 150 000-200 000 minor illnesses caused by dengue or chikungunya viruses; 4187 patients were hospitalized and diagnosed as having DHF and 4000 additional patients were treated in private clinics or at home. Shock occurred in about one-third of the hospitalized DHF patients.





### Transmission Chain of Dengue

Dengue virus is transmitted to man through mosquito bites and is therefore ranked among the arbovirus (arthropod-borne virus) diseases. Man is the main reservoir of the virus, though studies have shown that the monkey is the jungle reservoir in Malaysia.

#### The virus

The four serotypes of dengue virus (DEN-1, DEN-2, DEN-3, and DEN-4) are antigenically very similar to each other but they are different enough to elicit only partial cross-protection after infection by one of them. After an incubation period of 4-6 days (minimum 3, maximum 10), the virus is present in the blood of patients during the acute phase of the disease.

#### The vector

*Aedes aegypti* is the most efficient of the mosquito vectors because of its domestic habit. The female mosquito bites man during the day. After feeding on a person whose blood contains the virus, the female *A. aegypti* can transmit dengue either immediately, by a change of host when its blood meal is interrupted, or after an incubation period of 8-10 days, during which time the virus multiplies in its salivary glands. Dengue outbreaks have also been attributed to *Aedes albopictus*, *Aedes polynesiensis*, and several species of the *Aedes scutellaris* complex. Each of these species has its own particular geographical distribution and they are, in general, less efficient vectors than *A. aegypti*. Transovarian transmission of dengue viruses has been demonstrated in the laboratory and limited evidence has been obtained in the field, but its true importance in nature has not been established.

#### The host

In man, each of the four types of dengue virus has been associated with classical dengue and with dengue haemorrhagic fever. Studies in Thailand and Cuba have shown a consistently high association between dengue type 2 infection and shock syndrome; in the 1976-78 Indonesian and 1980-82 Malaysian epidemics dengue virus type 3 was frequently recovered from severe cases. DSS occurs with high frequency in two immunologically defined groups: (a) children who have experienced a previous dengue infection, and (b) infants with waning levels of maternal dengue antibody. The acute phase of





infection by dengue viruses, which lasts about 5–7 days, is followed by an immune response. The first attack gives only temporary and partial protection against the other three virus types, and secondary or sequential infections are possible after a rather short time.

### Pathology

Autopsy of cases of DHF shows some degree of haemorrhage; in order of frequency, this is found in the skin and subcutaneous tissue, in the mucosa of the gastrointestinal tract, and in the heart and liver. In general, subarachnoid or cerebral haemorrhage is rarely seen. The amount of haemorrhage, however, is not excessive. Serous effusion with a high protein content (mostly albumin) is commonly present in the pleural and abdominal cavities.

Light microscopy of the blood vessels shows no significant changes in the vascular walls. Occasionally, capillaries and venules in the afflicted organ system may show perivascular haemorrhage and perivascular infiltration by lymphocytes and mononuclear cells. Morphological evidence of intravascular clot formation in small vessels has been recognized in adults who had had severe haemorrhage.

In most fatal cases, with the exception of infants who had a primary dengue infection, the lymphoid tissue shows increasing activity of the B lymphocyte system, with active proliferation of plasma cells and lymphoblastoid cells, and very active germinal centres. There is evidence indicating proliferation of large immunoblasts and considerable turnover of the lymphocytes. The latter is manifested by a reduction in the white splenic pulps, lymphocytolysis, and marked lymphocytic phagocytosis.

In the liver, there is focal necrosis of the hepatic cells, swelling, the appearance of Councilman bodies, and hyaline necrosis of the Kupffer cells. Proliferation of mononuclear leukocytes, and less frequently of polymorphonuclear leukocytes, occurs in the sinusoids and occasionally in the portal areas. The lesions in the liver resemble those of yellow fever at around 72–96 hours, when parenchymal cell damage is limited.

Dengue virus antigen is found in cells predominantly in the liver, spleen, thymus, lymph nodes, and lung; these are Kupffer cells, sinusoidal lining cells, and alveolar lining cells of the lung.

Pathological studies have been made of the bone marrow, kidneys, and skin in non-fatal cases. In the bone marrow, depression of the marrow elements is observed. This rapidly improves when the fever subsides. The kidney shows an immune-complex type of glomerulonephritis. The complexes clear away after about 3 weeks and no residual change is seen.





The biopsy of skin rashes reveals perivascular oedema of the terminal microvasculature in the dermal papillae, with infiltration of lymphocytes and monocytes. Antigen-bearing mononuclear phagocytes can be found in the vicinity of the microvasculature of the dermal papillae. Deposition of complement, immunoglobulin, and fibrinogen on the vessel wall has also been described.

#### **Pathogenesis of Dengue Haemorrhagic Fever/Dengue Shock Syndrome**

Two main pathophysiological changes occur in DHF/DSS. One is an increased vascular permeability, giving rise to loss of plasma from the vascular compartment. This results in haemoconcentration, low pulse pressure, and other signs of shock if and when plasma loss becomes critical. The second change is a disorder in haemostasis which involves all three major factors: namely, vascular changes, thrombocytopenia, and coagulopathy.

A constant finding in DHF/DSS is activation of the complement system with profound depression of the C3 and C5 levels. Immune complexes have been described in DHF cases associated with secondary dengue infection, and these may contribute to the complement activation.

One factor that may contribute to the development of DHF/DSS is the enhancement by heterotypic antibodies of virus multiplication in macrophages. Such infected monocytes may then become the target of an immune-elimination mechanism which triggers the production by monocytes of chemical mediators of vascular permeability and the activation of complement and tissue thromboplastin, which in turn initiate intravascular blood coagulation. The mediators that increase vascular permeability and the precise mechanism(s) of the bleeding phenomena seen in dengue have not yet been identified. Further studies are needed.

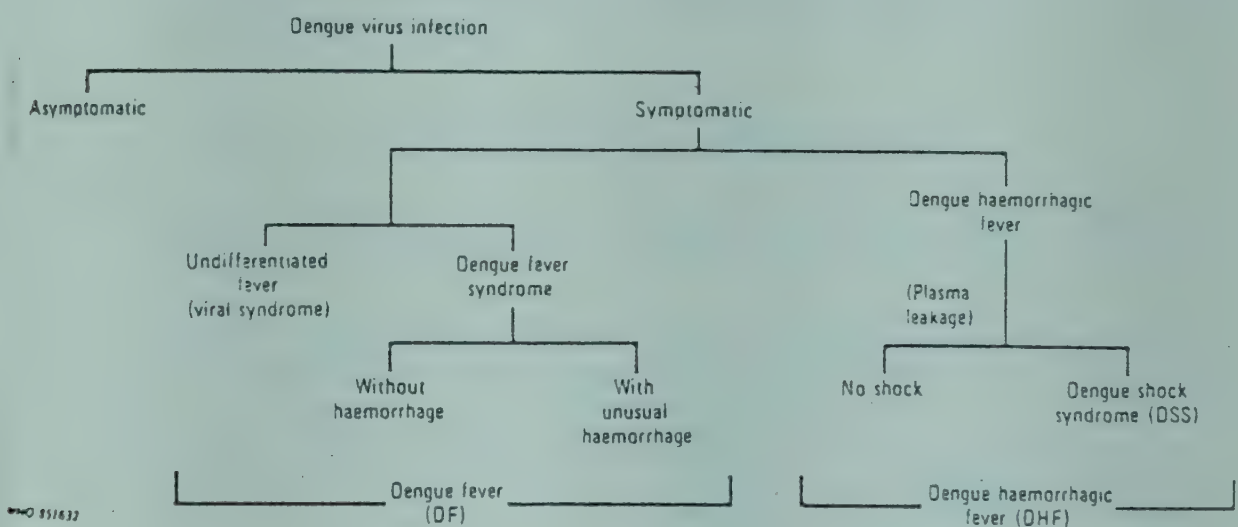




## 2. Clinical diagnosis

Dengue virus infections may be asymptomatic or may lead to undifferentiated fever, dengue fever, or dengue haemorrhagic fever (Fig. 1).

Fig. 1. Manifestations of the dengue syndrome



### Dengue Fever

The clinical features of dengue fever frequently depend on the age of the patient. Infants and young children may have an undifferentiated febrile disease with a maculopapular rash. Older children and adults may have either a mild febrile syndrome or the classical incapacitating disease with abrupt onset and high fever, severe headache, pain behind the eyes, muscle and joint pains, and rash. Skin haemorrhages (with a positive tourniquet test and/or petechiae) are not uncommon. Leukopenia is usually found and thrombocytopenia is occasionally observed. The case fatality rate is exceedingly low.





Many epidemics of dengue fever are accompanied by bleeding complications such as epistaxis, gingival bleeding, gastrointestinal bleeding, haematuria, and hypermenorrhoea. Unusually severe bleeding has caused death in some of these cases. It is important to differentiate cases of DF with unusual haemorrhage from cases of dengue haemorrhagic fever. Dengue fever must also be differentiated from chikungunya haemorrhagic fever (see Table 1).

### Dengue Haemorrhagic Fever

Typical cases of DHF, as seen in Asian countries, are characterized by four major clinical manifestations: high fever, haemorrhagic phenomena, hepatomegaly and, often, circulatory failure. Moderate to marked thrombocytopenia *with concurrent* haemoconcentration is a distinctive clinical laboratory finding. The major pathophysiological change that determines the severity of disease in DHF, and differentiates it from DF, is the *leakage of plasma*, as manifested by a rising haematocrit value and haemoconcentration.

#### Dengue haemorrhagic fever without shock

The illness commonly begins with a sudden rise in temperature, which is accompanied by facial flush and other non-specific

Table 1. Observed frequency of findings in classical dengue fever in adults and chikungunya and dengue virus infections in Thai children diagnosed as haemorrhagic fever<sup>a</sup>

Finding	Classical dengue in adults <sup>b</sup>	Chikungunya fever in Thai children	DHF in Thai children
Fever	++++	++++	++++
Positive tourniquet test	++	+++	++++
Petechiae or ecchymosis	+	++	++
Confluent petechial rash	0	0	+
Hepatomegaly	0	+++	++++
Maculopapular rash	++	++	+
Myalgia/arthralgia	+++		+
Lymphadenopathy	++	++	++
Leukopenia	++++	++++	++
Thrombocytopenia	++	+	++++
Shock	0	0	++
Gastrointestinal bleeding	0	0	+

<sup>a</sup> + = 1-25%; ++ = 26-50%; +++ = 51-75%; ++++ = 76-100%.

<sup>b</sup> The data have been taken from HALSTEAD, S. B. ET AL. *American journal of tropical medicine and hygiene*, 18: 984-996 (1969) and refer mainly to Caucasian adults.





constitutional symptoms resembling dengue fever, such as anorexia, vomiting, headache, and muscle or joint pains. Some patients complain of sore throat and an injected pharynx may be found on examination. Epigastric discomfort, tenderness at the right costal margin, and generalized abdominal pain are common. The temperature is typically high and continues so for 2-7 days, and then falls to a normal or subnormal level. Occasionally, the temperature may be as high as 40-41°C and febrile convulsions may occur.

The most common haemorrhagic phenomenon is a positive tourniquet test; easy bruising and bleeding at venepuncture sites are present in most cases. Fine petechiae scattered on the extremities, axillae, face, and soft palate may be seen during the early febrile phase. A confluent petechial rash with characteristic small round areas of normal skin is sometimes seen in convalescence, when the temperature has become normal. A maculopapular or rubella-type rash may be observed early or late in the disease. Epistaxis and gum bleeding are less common. Mild gastrointestinal haemorrhage is occasionally observed.

The liver is usually palpable early in the febrile phase. The size of the liver varies from just-palpable to 2-4 cm below the costal margin. Liver size is not correlated with disease severity but hepatomegaly is more frequent in shock cases. The liver is tender but jaundice is not usually observed even in patients with a big, tender liver. Splenomegaly is rarely observed in small infants; however, the spleen is often noted to be prominent on X-ray examination.

In mild or moderate cases, after fever subsides, all signs and symptoms abate. Lysis of fever may be accompanied by profuse sweating and mild changes in pulse rate and blood pressure, together with coolness of extremities and skin congestion. These changes reflect mild and transient circulatory disturbances as a result of some degree of plasma leakage. Patients usually recover spontaneously or after fluid and electrolyte therapy.

### Dengue shock syndrome (DSS)

In severe cases, after fever of a few days' duration the patient's condition suddenly deteriorates. At the time of, or shortly after, the fall in temperature, between the 3rd and the 7th day of the disease, there are signs of circulatory failure: the skin becomes cool, blotchy, and congested; circumoral cyanosis is frequently observed; and the pulse becomes rapid. Although some patients may appear lethargic, they become restless and then rapidly go into a critical stage of shock. Acute abdominal pain is a frequent complaint shortly before the onset of shock.





Shock is characterized by a rapid, weak pulse with narrowing of the pulse pressure (20 mmHg (2.7 kPa) or less, regardless of the pressure levels) or hypotension, with cold, clammy skin and restlessness. Patients in shock are in danger of dying if appropriate treatment is not promptly given. Patients may pass into a stage of profound shock, both blood pressure and pulse becoming imperceptible. Most patients remain conscious almost to the terminal stage. The duration of shock is short; the patient may die within 12–24 hours or recover rapidly following appropriate antishock therapy. Alternatively, uncorrected shock may give rise to a more complicated course with metabolic acidosis, severe bleeding from the gastrointestinal tract and various other organs, and a poor prognosis. Patients with intracranial haemorrhage may go into coma.

Convalescence in DHF with or without shock is short and uneventful. Even in cases with profound shock, once the shock is overcome, the surviving patients recover within 2–3 days. Return of appetite is a good prognostic sign. A common finding in convalescence is bradycardia or sinus arrhythmia; absolute bradycardia is occasionally seen.

#### Clinical manifestations in adults

Experience in Cuba in 1981 showed that in adults the infection was usually manifested by the clinical symptoms of classical dengue fever: high fever, retro-orbital headache, myalgia, and asthenia. Less frequently, patients demonstrated thrombocytopenia and haemorrhagic manifestations. Overt shock was rare, but was severe when it did occur; it was found mostly in the elderly or in adults with a history of allergy or chronic pulmonary or cardiovascular disease. In one series of 1000 adult cases studied in Cuba, the persons who were severely ill usually showed thrombocytopenia and haemoconcentration. In the five cases with hypovolaemic shock not associated with haemorrhage, the disease responded, as in children, to vigorous fluid replacement. Hypovolaemia and hypotension secondary to gastrointestinal bleeding were seen in two adult patients; one died. Serious bacterial infections occasionally complicated the dengue illness; in this series, one of the two adults with a fatal outcome had a severe respiratory tract infection.

#### Clinical laboratory findings

Thrombocytopenia and haemoconcentration are rather constant findings in DHF. A platelet count of below  $100\,000/\text{mm}^3$  is usually found between the 3rd and 8th day. Haemoconcentration—indicating plasma leakage—is almost always present, even in non-shock cases; it is always more severe, however, in shock cases.





Other common findings are hypoproteinaemia, hyponatraemia, and mildly elevated serum aspartate aminotransferase<sup>1</sup> and blood urea nitrogen levels. Metabolic acidosis may be found in cases with prolonged shock. Serum complement levels are reduced.

The white blood cell count is variable, ranging from leukopenia to mild leukocytosis. Lymphocytosis with atypical lymphocytes is a common finding. A transient mild albuminuria is sometimes observed. Occult blood is often found in the stool. In most cases, assays of coagulation and fibrinolytic factors show reductions in fibrinogen, prothrombin, factor VIII, factor XII, antithrombin III, and  $\alpha$ -antiplasmin ( $\alpha$ -plasmin inhibitor). In severe cases with liver dysfunction, reductions are observed in the vitamin-K-dependent prothrombin family, such as factors V, VII, IX, and X. About one-third of shock cases have a prolonged prothrombin time (PT) and about half of these patients exhibit a prolonged partial thromboplastin time (PTT).

#### Dengue Infections with Central Nervous System Manifestations

Some patients with DF or DHF present central nervous system manifestations such as convulsions, spasticity, or a non-transient (more than 8 hours) change in consciousness. Five cases of transient paresis with hyporeflexia have been observed in Indonesia and Malaysia. A fatal case with encephalitic manifestations associated with dengue virus type 3 infection has also been seen in Indonesia. The cerebrospinal fluid findings in these cases were normal. Further studies are needed to identify what factors contributed to these unusual manifestations.

#### Criteria for Clinical Diagnosis of Dengue Haemorrhagic Fever/Dengue Shock Syndrome

The following clinical manifestations have been selected as indicating a clinical diagnosis of DHF. *The use of these criteria may help to avoid overdiagnosis of the disease.*

##### Clinical

- (a) Fever—acute onset, high, continuous, and lasting 2–7 days.
- (b) Haemorrhagic manifestations, including at least a positive

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<sup>1</sup> Previously known as serum glutamic oxaloacetic transaminase (SGOT).





tourniquet test.<sup>1</sup> Any of the following may be present:

- petechiae, purpura, ecchymosis
  - epistaxis, gum bleeding
  - haematemesis and/or melaena.
- (c) Enlargement of liver (observed at some stage of the illness in 90–96% of Thai children with DHF).
- (d) Shock—manifested by rapid and weak pulse with narrowing of the pulse pressure (20 mmHg (2.7 kPa) or less) or hypotension, with the presence of cold, clammy skin and restlessness.

### Laboratory

- (a) Thrombocytopenia ( $100\,000/\text{mm}^3$  or less).<sup>2</sup>
- (b) Haemoconcentration; haematocrit increased by 20% or more of recovery value.

The first two clinical criteria plus thrombocytopenia and haemoconcentration or a rising haematocrit are sufficient to establish a clinical diagnosis of DHF. When there is anaemia or severe haemorrhage, pleural effusion (chest X-ray) and/or hypoalbuminaemia provide supporting evidence of plasma leakage.

Shock with a high haematocrit (except in patients with severe bleeding) and marked thrombocytopenia supports a diagnosis of DHF/DSS.

The relationship of clinical syndromes with physical and laboratory findings is shown in Fig. 2.

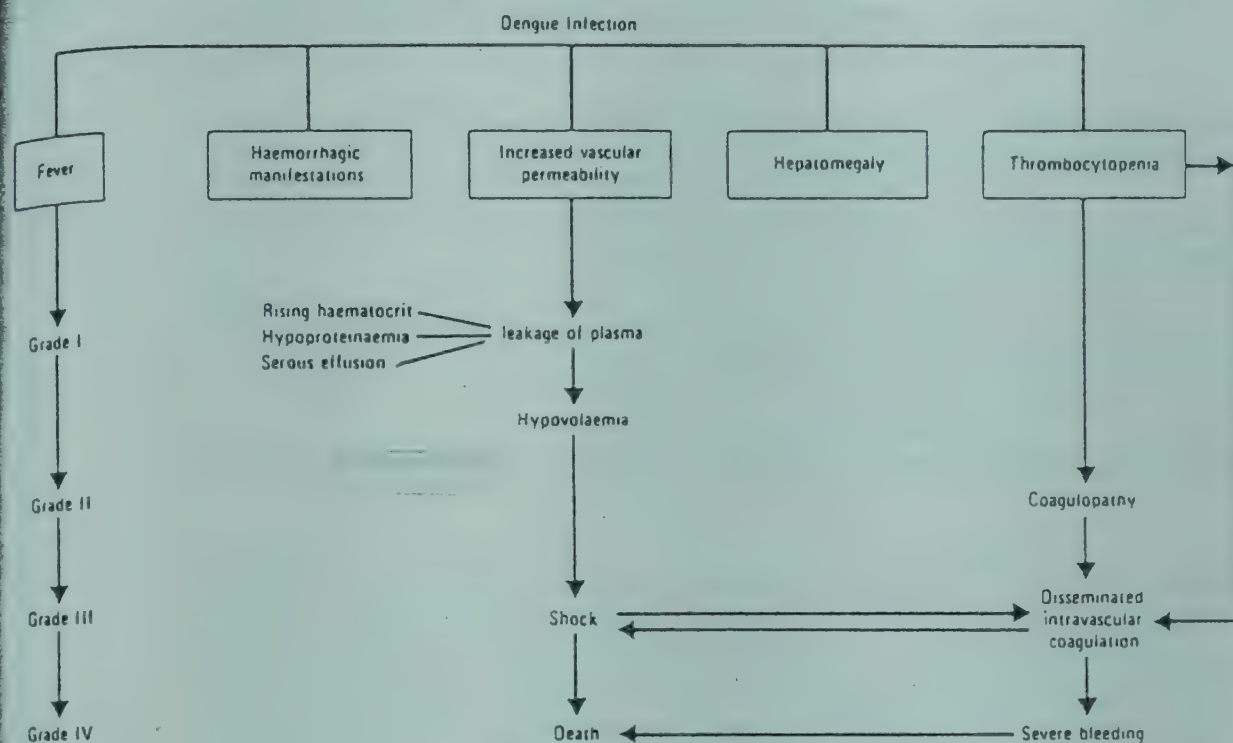
<sup>1</sup> The standard method using a blood pressure cuff is recommended. In DHF patients, the test usually gives a definite positive result, i.e., more than 20 petechiae per 2.5-cm (1-inch) square. The test may be negative or mildly positive during the phase of profound shock. It usually becomes positive, sometimes strongly positive, if the test is done after recovery from shock.

<sup>2</sup> Direct count using a phase-contrast microscope (normal  $200\,000$ – $500\,000/\text{mm}^3$ ). In practice, for outpatients, an approximate count from a peripheral blood smear is acceptable. In normal persons, 4–10 platelets per oil-immersion field (an average reading from 10 fields is recommended) indicates an adequate platelet count. An average of 2–3 per oil-immersion field or less is considered low (i.e.,  $< 100\,000/\text{mm}^3$ ).





Fig. 2. The spectrum of dengue haemorrhagic fever



### Case Definition

For reporting purposes, the following criteria should be used to establish a dengue diagnosis:

#### Dengue haemorrhagic fever

1. Fever.
2. Haemorrhagic manifestations including at least a positive tourniquet test (except in shock cases), and perhaps minor or major bleeding phenomena.
3. Thrombocytopenia ( $100\,000/\text{mm}^3$  or less).
4. Haemoconcentration: haematocrit increased by 20% or more, or objective evidence of increased capillary permeability.

#### Dengue shock syndrome

1. All the above criteria, plus
2. Hypotension or narrow pulse pressure (20 mmHg (2.7 kPa) or less).





### Grading the Severity of Dengue Haemorrhagic Fever

The severity of DHF is classified into four grades:

DHF	Grade I—	Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test.
		Grade II— Spontaneous bleeding in addition to the manifestations of Grade I patients, usually in the form of skin and/or other haemorrhages.
	DSS	Grade III— Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness.
		Grade IV— Profound shock with undetectable blood pressure and pulse.

The presence of thrombocytopenia with concurrent haemoconcentration differentiates Grade I and II DHF from dengue fever.

Grading the severity of the disease has been found clinically and epidemiologically useful in DHF epidemics in children in the South-East Asia and Western Pacific Regions. However, it may not be applicable to dengue in adults.

### Differential Diagnosis of Dengue Haemorrhagic Fever/Dengue Shock Syndrome

Early in the febrile phase, the differential diagnosis includes a wide spectrum of viral and bacterial infections. Chikungunya fever may be difficult to differentiate clinically from mild DHF without shock (see Table 2 and Table 3).

By the third or fourth day, usually before shock occurs, the laboratory findings essential for diagnosis can be observed and should help establish the diagnosis under epidemic conditions. When shock develops with other manifestations, the clinical diagnosis of DHF can be made with more confidence.

The presence of marked thrombocytopenia with concurrent haemoconcentration differentiates DHF/DSS from other diseases such as endotoxic shock from bacterial infection, or meningococcaemia. In patients with severe bleeding, evidence of pleural effusion and/or hypoproteinaemia may indicate plasma leakage.

### Record Sheet

A model record sheet for DHF is presented in Annex 2.





Table 2. Non-specific constitutional symptoms observed in haemorrhagic fever patients with dengue and chikungunya virus infection<sup>a</sup>

Symptom	DHF (%)	Chikungunya fever (%)
Injected pharynx	98.9	90.3
Vomiting	57.9	59.4
Constipation	53.3	40.0
Abdominal pain	50.0	31.6
Headache	44.6	68.4
Generalized lymphadenopathy	40.5	30.8
Conjunctival injection	32.8 <sup>b</sup>	55.6 <sup>b</sup>
Cough	21.5	23.3
Restlessness	21.5	33.3
Rhinitis	12.8	6.5
Maculopapular rash	12.1 <sup>b</sup>	59.6 <sup>b</sup>
Myalgia/arthritis	12.0 <sup>b</sup>	40.0 <sup>b</sup>
Enanthema	8.3	11.1
Abnormal reflex	6.7	0.0
Diarrhoea	6.4	15.6
Palpable spleen	6.3 <sup>c</sup>	3.1 <sup>c</sup>
Coma	3.0	0.0

<sup>a</sup> Based on: NIMMANNITYA, S. ET AL. *American journal of tropical medicine and hygiene*, 18: 954-971 (1969).

<sup>b</sup> Statistically significant difference.

<sup>c</sup> Infants under 6 months.

Table 3. Criteria for differential diagnosis of dengue haemorrhagic fever and chikungunya haemorrhagic fever<sup>a</sup>

Criteria	DHF (%)	Chikungunya fever (%)
Duration of fever:		
2-4 days	23.6	62.5
5-7 days	59.0	31.2
> 7 days	17.4	6.3
Haemorrhagic manifestations:		
positive tourniquet test	83.9	77.4
scattered petechiae	46.5	31.3
confluent petechial rash	10.1	0.0
epistaxis	18.9	12.5
gum bleeding	1.5	0.0
melaena/haematemesis	11.8	0.0
Hepatomegaly	90.0	75.0
Shock	35.2	0.0

<sup>a</sup> Based on: NIMMANNITYA, S. ET AL. *American journal of tropical medicine and hygiene*, 18: 954-971. (1969).





### 3. Treatment

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#### General Considerations

The major pathophysiological abnormality seen in DHF/DSS is an acute increase in vascular permeability that leads to leakage of plasma. Plasma volume studies reveal a reduction of more than 20% in severe cases. Supporting evidence of plasma leakage includes: serous effusion found post mortem, pleural effusion on X-ray, haemoconcentration, and hypoproteinaemia. The fact that no destructive or inflammatory vascular lesions are observed suggests that transient, functional vascular changes are due to a short-acting pharmacological mediator. In severe cases, the onset of shock is acute and haematocrit rises sharply as plasma escapes through the endothelium. Hypovolaemic shock leads to tissue anoxia, metabolic acidosis, and death if uncorrected.

Haemostatic changes in DHF involve three factors: vascular changes, thrombocytopenia, and coagulation disorders. All patients demonstrate an increase in capillary fragility (positive tourniquet test) and moderate to marked thrombocytopenia. Almost 80% of patients with DSS and 17% of non-shock cases have an abnormal coagulogram suggesting disseminated intravascular coagulation (DIC), as evidenced by concomitant thrombocytopenia, prolonged partial thromboplastin time (PTT), decreased fibrinogen level, and increased fibrinogen degradation product (FDP). In cases of prolonged uncontrolled shock, DIC may cause important clinical bleeding and may play an important part in the development of lethal shock. About one-third of shock cases, mostly those with refractory shock, present bleeding, mainly from the gastrointestinal tract. Gastrointestinal haemorrhage is a fairly constant finding at autopsy in the majority of patients who die.

Early and effective replacement of losses with plasma, plasma expander, and/or fluid and electrolyte solution results in a favourable outcome in most cases. With adequate fluid administration, DSS is rapidly reversible. Rapid replacement will usually





prevent clinical DIC. Prognosis depends upon early recognition of shock, based on careful monitoring.

It is not necessary to hospitalize all suspected cases of DHF, since shock may develop in only about one-third of patients. The constant finding that a drop in the platelet count usually precedes the rise in haematocrit is of great diagnostic and prognostic value. In order to be able to recognize the early signs of shock, and thus to take preventive action, parents should be advised to bring the patient back for repeat platelet and haematocrit determinations. A watch should also be kept for any signs of clinical deterioration or warning signs of shock, e.g., restlessness and/or lethargy, acute abdominal pain, cold extremities, skin congestion, or oliguria, usually on or after the third day of illness.

### Dengue Haemorrhagic Fever Without Shock

Thirst and dehydration result from high fever, anorexia, and vomiting; thus fluid intake by mouth should be ample, as tolerated. Electrolyte replacement solution as used in treatment of diarrhoeal disease<sup>1</sup> and/or fruit juice is preferable to plain water.

During the febrile phase there is a risk of convulsions, and antipyretic drugs may be indicated in patients with hyperpyrexia. *Salicylates should be avoided* since they may cause bleeding and acidosis. Paracetamol is preferable, in the following doses:

under 1 year	:	60 mg/dose
1-3 years	:	60-120 mg/dose
3-6 years	:	120 mg/dose
6-12 years	:	240 mg/dose

Patients should be closely observed for early signs of shock. The critical period is during the transition from the febrile to the afebrile phase which usually occurs after the third day. Haematocrit determinations are an essential guide to therapy since they reflect the degree of plasma leakage and the need for

<sup>1</sup> If the WHO oral rehydration solution (90 mmol of Na per litre) is to be used in children under 2 years of age, additional fruit juice or water should be given in the proportion of one volume of fruit juice (or plain water) for every two volumes of ORS. The WHO oral rehydration solution consists of:

Sodium chloride	3.5 g
Trisodium citrate, dihydrate	2.9 g
Potassium chloride	1.5 g
Glucose	20.0 g

dissolved in 1 litre of potable water.





intravenous fluid. Haemoconcentration usually precedes the blood pressure and pulse changes. Haematocrit should be determined daily from the third day until the temperature becomes normal for 1 or 2 days. If haematocrit determination is not possible, haemoglobin determination may be carried out as an alternative, but this is less sensitive.

Parenteral fluid therapy can be given in an outpatient department rehydration unit in mild or moderate cases, when vomiting produces or threatens to produce dehydration or acidosis or when there are signs of haemoconcentration. The fluids to be given are similar in volume and composition to those used in the intravenous treatment of diarrhoea with moderate dehydration. The schedule shown in Table 4 is recommended as a guideline. The fluid should consist of the following:

- $\frac{1}{2}$ – $\frac{1}{3}$  of the total fluid as physiological saline solution (PSS), the remainder as 5% glucose in water (50 g/litre). In cases of acidosis:  $\frac{1}{4}$  of the total fluids should consist of 0.167 mol/litre sodium bicarbonate, i.e.,  $\frac{3}{4}$  (PSS + glucose) +  $\frac{1}{4}$  sodium bicarbonate.
- For fluid therapy in DHF/DSS use: Ringer's lactate (RL), 5% glucose in PSS, 5% glucose in  $\frac{1}{2}$  PSS, 5% glucose in  $\frac{1}{2}$  RL, or 5% glucose in  $\frac{1}{3}$  PSS. The choice of fluid depends on the age of the child and the degree of dehydration.

Table 4. Intravenous fluid infusion for moderate dehydration<sup>a</sup>

ml per lb body weight

	Weight on admission			
	< 15 lb	16–25 lb	26–40 lb	> 40 lb
First day	100	75	60	40
Second day	75	60	40	40
Third day	60	40	40	40

ml per kg body weight

	Weight on admission			
	< 7 kg	7–11 kg	12–18 kg	> 18 kg
First day	220	165	132	88
Second day	165	132	88	88
Third day	132	88	88	88

<sup>a</sup> Based on: *Pediatric clinics of North America*, 11: 1093 (1964).





The fluids listed above are calculated for administration over a 24-hour period. If the child seems severely dehydrated, half of the calculated fluid is given in the first 8 hours and the second half in the next 16 hours. *During rapid administration of the fluids it is especially important to watch for signs of cardiac failure.*

Written orders should be explicit as to the type of solution and the rate of administration. A rough estimate of flow may be derived from the formula:

$$\text{ml/hour} = (\text{drops/min}) \times 3$$

Patients should be hospitalized and treated immediately if there are any of the following signs and symptoms of shock:

- restlessness/lethargy
- cold extremities and circumoral cyanosis
- rapid and feeble pulse
- narrowing of pulse pressure (20 mmHg or less) or hypotension
- sudden rise of haematocrit or continuously elevated haematocrit despite administration of I.V. fluids.

### Dengue Shock Syndrome

Shock is a medical emergency. Volume replacement is the most important measure. The immediate administration of intravenous fluid to expand plasma volume is essential. Children may go into and out of shock during a 48-hour period. Close observation 24 hours a day is imperative.

#### Immediate replacement of plasma loss

Start initial intravenous fluid therapy with Ringer's lactate or isotonic saline solution at the rate of 20 ml/kg body weight. Run fluid as rapidly as possible. Positive pressure may be necessary. In case of continued or profound shock, plasma or plasma expander (Dextran, of medium relative molecular mass, in PSS) is given following the initial fluid at a rate of 10–20 ml/kg per hour. In most cases not more than 20–30 ml of plasma per kg of body weight (or 10–15 ml of Dextran/kg) is needed. Fluid administration should be continued at this constant rate (10–20 ml/kg per hour) until improvement in vital signs is apparent. Dextran 40 is effective as a substitute for plasma.





### Continued replacement of plasma loss based on frequent microhaematocrit determinations

Intravenous fluid (5% Dextran,  $\frac{1}{2}$  Ringer's lactate, or  $\frac{1}{2}$  PSS) is continued even when there is a definite improvement in vital signs and a declining haematocrit. The rate of fluid replacement should be slowed down to 10 ml/kg per hour and adjusted thereafter to the rate of plasma loss, which may continue for 24 or 48 hours. Determination of central venous pressure may also be necessary in the management of severe cases of shock that are not easily reversible.

Intravenous fluids *should be discontinued* when the haematocrit level drops to around 0.4 (40%) and the patient's appetite returns. A good urine flow indicates sufficient circulating fluid. In general, there is no need for fluid therapy for more than 48 hours after the termination of shock. Reabsorption of extravasated plasma takes place (manifested by a further drop in haematocrit after intravenous fluid has been stopped) and may cause hypervolaemia, pulmonary oedema, or heart failure if more fluid is given. It is extremely important that a drop in haematocrit at this stage is not interpreted as a sign of internal haemorrhage. Strong pulse and blood pressure (with wide pulse pressure) and diuresis are good vital signs during this reabsorption phase. They rule out the likelihood of gastrointestinal haemorrhage, which is found mostly during the shock stage.

### Other electrolyte and metabolic disturbances that may need specific correction

Hyponatraemia occurs commonly and metabolic acidosis occasionally. Electrolyte levels and blood gases should be determined periodically in severely ill patients and patients who do not seem to respond as promptly as expected. This will provide an estimate of the magnitude of the electrolyte (sodium) deficit and help determine the presence and degree of acidosis. Acidosis, in particular, if uncorrected may lead to disseminated intravascular clotting and to a more complicated course. The use of heparin may be indicated in some of these cases but *extreme caution* should be exercised. In general, early volume replacement and early correction of acidosis with sodium bicarbonate result in a favourable outcome and avoid the need for heparin.

### Sedatives

Sedative therapy is needed in some cases to restrain an agitated child. Hepatotoxic drugs should be avoided. Chloral hydrate, orally





or rectally, is highly recommended in a dose of 12.5–50 mg/kg body weight (but not more than 1 g) *as a single hypnotic dose*.

### Oxygen therapy

Oxygen therapy should be given to all patients in shock, but the staff involved should be aware that the oxygen mask or tent may increase apprehension.

### Blood transfusion

Blood grouping and matching should be carried out as a *routine* precaution for every patient in shock. Blood transfusion is indicated in cases with significant clinical bleeding.

It may be difficult to recognize internal bleeding in the presence of haemoconcentration. A drop in the haematocrit (e.g., from 0.5 (50%) to 0.4 (40%)) with no clinical improvement despite adequate fluid administration indicates significant internal haemorrhage. Fresh whole blood is preferable and the amount of blood given should be such that normal red blood cell concentration is not exceeded. Fresh frozen plasma and/or concentrated platelets may be indicated in some cases when consumptive coagulopathy causes massive bleeding. DIC is usual in severe shock and it may play an important part in the development of massive bleeding and lethal shock. The results of haematological tests (prothrombin time (PT) and partial thromboplastin time (PTT)) should be studied in all shock cases to document the onset and severity of DIC, which determines the prognosis.

### Essential laboratory tests

In assessing the patient, the following tests are recommended:

- Serum electrolytes and blood gas studies
- Platelet count, prothrombin time, partial thromboplastin time, and thrombin time
- Liver function tests: serum aspartate aminotransferase,<sup>1</sup> serum alanine aminotransferase,<sup>2</sup> and serum proteins.

### Monitoring of anti-shock therapy

Frequent recording of vital signs and haematocrit determination are important in evaluating the results of treatment. If patients show

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<sup>1</sup> Previously known as serum glutamic-oxaloacetic transaminase (SGOT).

<sup>2</sup> Previously known as serum glutamic-pyruvic transaminase (SGPT).





any signs announcing a secondary shock, vigorous anti-shock therapy should be instituted promptly. Patients should be under constant and careful observation until there is reasonable certainty that the danger has passed. In practice:

- The pulse, the blood pressure, the respiration, and the temperature should be recorded every 15-30 minutes or more often, until shock is overcome.
- Haematocrit and haemoglobin levels should be determined every 2 hours for the first 6 hours, then every 4 hours until stable.
- A fluid balance sheet should be kept, recording the type of fluid given and the rate and amount, to evaluate the adequacy of replacement and correction of fluid and electrolytes. Frequency and volume of urine output should also be recorded.

#### Outpatient and Inpatient Flow Charts

Flow charts are included in this book (Annexes 3 and 4) to provide guidance in the diagnosis and treatment of dengue haemorrhagic fever/dengue shock syndrome. These charts may be used by the physician to familiarize himself with the decisions involved in providing appropriate medical care to these patients. Judgement must be applied to the application of these flow charts. The flow charts may also be useful for training and guiding nurses, medical students, and paramedical personnel in the identification and treatment of severe cases of dengue virus infection. They are designed for primary and secondary health units in which sophisticated electronic monitoring equipment is not available. If highly technical intensive care is available, judgement must be used to determine the best, but least invasive, treatment programme for each patient.



## 4. Laboratory diagnosis

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There are two basic methods for establishing a routine laboratory diagnosis of dengue: (a) isolation of the virus, or (b) demonstration of a rising titre of serum dengue antibodies. Isolation of the virus is the more definitive approach, but the techniques at present available require a relatively high level of technical skills and equipment. Serological tests are simpler and more rapid. However, serological cross-reactions between antibodies to dengue and other flaviviruses may cause occasional false positive diagnoses. Also, accurate identification of the infecting dengue serotype is impossible using paired sera with routine serological methods (haemagglutination inhibition or complement fixation).

An essential aspect of the laboratory diagnosis of dengue is proper collection, storage and shipment of specimens.

### Collection of Specimens

Health workers should be informed of the appropriate procedures for collecting specimens:

- Blood samples should be drawn from suspected DHF cases (a) as soon as possible after hospital admission or attendance at the clinic (serum specimen S1); (b) shortly before discharge from the hospital (serum specimen S2); and, (c) if possible, 14–21 days after disease onset (serum specimen S3). Failure to leave an interval of 10–14 days between S1 and S2 may prevent the serological diagnosis of primary dengue infections.
- An abbreviated case history, including the following minimum information, should accompany specimens: name and number of patient, address, age, sex, date of onset of illness, date of hospitalization, date of collection of specimen, and brief clinical findings. A model of a suitable request form for arbovirus laboratory examination, and a reporting form, are given in Annex 5.

Blood may be collected either in tubes or vials or on filter-paper.





**Blood collection in tubes or vials**

- Aseptically collect 2-5 ml of venous blood.
- Use adhesive tape marked with pencil or indelible ink, or a typewritten self-adhesive label to identify the container. Name of patient, identification number and date of collection must be indicated.
- Use tubes or vials with screw-caps if possible. Fix the cap with adhesive tape, wax or other sealing material to prevent leakage during transport.
- Ship to laboratory on wet-ice as soon as possible. Do not send frozen whole blood, as haemolysis may interfere with laboratory tests.
- If there will be more than a 24-hour delay before the specimens can be submitted, the serum should be separated from the red blood cells and stored frozen.

**Blood collection on filter-paper<sup>1</sup>**

- With a pencil, write the patient's initials or number on two or three discs or strips of standardized absorbent paper.<sup>2</sup>
- Collect sufficient finger-tip blood (or venous blood in a syringe) on the filter-paper to *saturate it through to the reverse side*.

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<sup>1</sup> If blood is collected on filter-paper discs, one of the recommended methods for eluting the blood and preparing it for the HI test is as follows:

1. Elute the disc for 60 min at room temperature or at 4°C overnight in 1 ml of kaolin in borate saline (125 g/litre), pH 9.0, in a test-tube.
2. After elution, keep the tube at room temperature for 20 min, shaking periodically.
3. Centrifuge for 30 min at 600 g.
4. For HI tests using goose erythrocytes, without removing the kaolin add 0.05 ml of 50% suspension of goose cells to the tube, shake without disturbing the pellet, and incubate at 37°C for 30 min.
5. Add 1 ml of borate saline, pH 9.0, to the tube.
6. Centrifuge at 600 g for 10 min and decant the supernatant.
7. This is approximately equivalent to a 1:30 serum dilution.
8. Each laboratory must standardize the filter-paper technique against results with venous blood in a panel of individuals.

<sup>2</sup> Whatman No. 3 filter-paper discs 12.7 mm ( $\frac{1}{2}$  inch) in diameter are suitable for this purpose, or Nobuto Type 1 blood-sampling paper made by Toyo Roshi Kaisha Ltd., Tokyo, Japan.





- Allow the discs or strips to dry in a place that is protected from direct sunlight and insects. Preferably, the blood-soaked papers should be placed in a stand which allows aeration of both sides. For unusually thick papers, a drying chamber may be useful, e.g., dessicator jar, air-conditioned room, or warm-air incubator.
- Place the dried strips in plastic bags and staple them to the laboratory examination request form. Store without refrigeration. Dried filter-paper discs may be sent through the mail.

### Isolation of Virus

Isolation of dengue virus from clinical specimens can be accomplished in many cases. Major factors favouring successful isolation are (a) taking the specimen early in the course of the disease and (b) delivering it promptly to the virus laboratory.

Materials that often contain virus and may be suitable for use in determining whether dengue virus is present or not, can be obtained as follows:

<i>Source</i>	<i>Material</i>
Patient	Serum, plasma, or washed buffy coat
Autopsy	Homogenized tissues, especially liver, spleen, lymph nodes, and thymus
Vector mosquitos	Homogenized, pooled mosquitos

The material thus obtained is inoculated in various ways and the outcome observed. The different methods of inoculation and the results confirming the presence of dengue virus are shown in Table 5.

The choice of the method of identification to be used will depend on: (1) local availability of mosquitos, cells, and mice; and (2) patient population characteristics. As far as sensitivity is concerned, inoculation of serum or plasma into mosquitos or mosquito cell cultures is the most sensitive method with patients who present early in the course of the disease (3 days of fever or less) and/or with a low HI antibody titre ( $< 1:640$ ). In contrast, cocultivation of leukocytes with mammalian cells is the most sensitive method with patients who present late (after 5 days or more) and/or with a high HI antibody titre ( $> 1:640$ ) in the acute blood specimen.

To identify the different dengue virus serotypes, mosquito head squashes, suckling mouse brain touch preparations, and slides of infected cultures are made by means of fluorescein isothiocyanate (FITC)-labelled antimouse antibodies (obtainable from suppliers of





Table 5. Methods of inoculation used in confirming presence of dengue virus

Method of inoculation	Result confirming presence of dengue virus
Inoculation of mosquitos <sup>a</sup>	Presence of antigen in head squashes demonstrated by IF <sup>b</sup>
Inoculation of various mammalian <sup>c</sup> or insect cell cultures	(a) Type-specific identification after IF staining <sup>b</sup> (b) Cytopathic effect in cells (c) Plaque formation
Intracranial inoculation of suckling mice	(a) Presence of antigen in brain on day 7 demonstrated by IF <sup>b</sup> (b) Abnormal behaviour

<sup>a</sup> Mosquito tissues may be issued as CF antigen in typing tests.

<sup>b</sup> Immunofluorescence.

<sup>c</sup> Buffy coat can be co-cultivated with cell lines.

biological materials). These are then treated with specific mouse monoclonal antibodies.<sup>1</sup>

For short periods of storage (up to 24 hours) materials to be issued for virus isolation are usually kept at +4 to +8°C; for longer storage, the material should be frozen at -70°C. In the latter case they should be maintained so that thawing does not occur. Whenever possible, original materials (viraemic serum of infected mosquito pools) as well as laboratory-passaged materials should be preserved for future study.

If isolation from living leukocytes is to be attempted, heparinized blood samples should be delivered to the laboratory within a few hours.

It is essential for health workers interested in making a diagnosis by means of viral isolation to make contact with the appropriate virology laboratory prior to the collection of specimens. The acquisition, storage, and shipment of the samples can then be organized to give the best chance of successful isolation.

### Serological Tests

There are two types of serum response pattern in acute dengue infection—primary and secondary. A *primary* response is seen in individuals who are non-immune to flaviviruses (i.e., have never been infected with a flavivirus and have never been inoculated with a flavivirus vaccine, such as 17D yellow fever or Japanese encephalitis vaccine).

<sup>1</sup> Obtainable from the Division of Vector-Borne Viral Diseases, Centers for Disease Control, Fort Collins, CO 80522, USA.

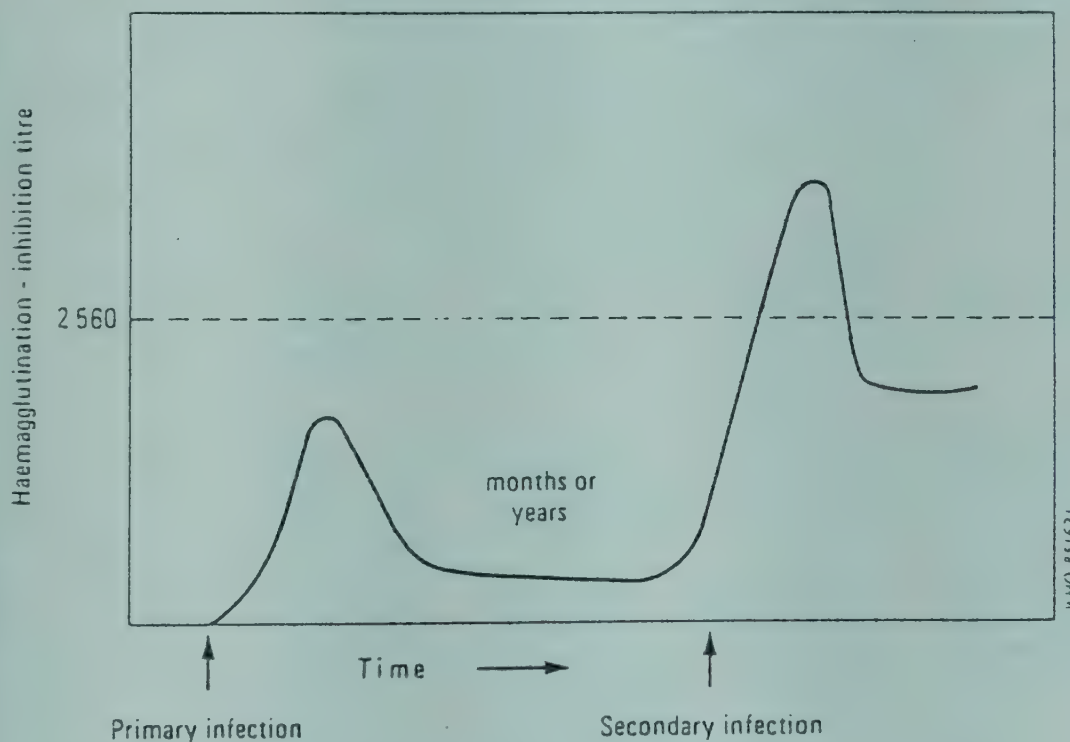




A *secondary* seroresponse pattern occurs in an individual with an acute dengue infection who has had a previous flavivirus infection. Secondary seroresponse patterns may occur as a result of immunity to other flaviviruses (such as Japanese encephalitis or yellow fever) or to a different dengue virus serotype (for example, dengue type 2 infection in a person immune to dengue type 1). Once infected with a given dengue serotype, an individual can never become infected with that serotype again.

In a primary dengue infection, the antibody titre rises slowly to a modest level and is relatively monospecific (i.e., the titre is higher against the infecting dengue serotype than against other antigens). In secondary infections, the antibody titre rises rapidly to very high levels, and there are reactions with a wide variety of flavivirus antigens (Fig. 3). Unusually high titres are found only in sera taken from patients experiencing an acute secondary infection.

Fig. 3. Primary and secondary immunological responses in dengue infections



#### Haemagglutination inhibition (HI) test<sup>1</sup>

Dengue viruses agglutinate erythrocytes (RBC) from geese and certain other species and trypsinized human group O cells. The HI test is based on the ability of dengue antibody to inhibit this haemagglutination. It is the most widely used serological test for

<sup>1</sup> HA antigens of dengue types 1-4, chikungunya, and Japanese encephalitis can be purchased from the Virus Research Institute, Yodse, Bangkok, Thailand.





dengue antibody. The recommended technique is that of Clarke & Casals<sup>1</sup> which has been adapted to microtitration equipment and is described in most manuals of virology.

- Sera should be extracted with kaolin or with acetone to remove non-specific inhibitors and then absorbed with goose RBC to remove non-specific agglutinins.
- Ideally, all sera (S1, S2, S3) should be tested against each of the four dengue antigens in the same run using 4-8 haemagglutinating units. However, a single test using a single broadly-reactive antigen (usually dengue type 1 or type 4) can be performed instead, with only a slight loss of sensitivity. If the paired sera have no antibody or do not show a significant antibody rise, the specimens may then be retested against all four dengue antigens.
- Sera should be tested against chikungunya antigen where this virus is known to be endemic.<sup>1</sup>
- Known positive and negative dengue sera should be included in each test to standardize the results and maintain quality control. Standard reference sera are available from a WHO Collaborating Centre (see Annex 6).
- The interpretations of dengue antibody responses in the HI test are shown in Table 6.<sup>2</sup>

Table 6. Interpretation of dengue HI antibody responses

Antibody responses	S1-S2 interval	Convalescent titre (any dengue antigen)	Interpretation
≥ 4× rise	≥ 7 days	≤ 1:1280	Definite infection, primary
≥ 4× rise	any specimen	≥ 1:2560	Definite infection, secondary
≥ 4× rise	< 7 days	≤ 1:1280	Definite infection, possible primary or secondary
no change	any specimen	≥ 1:2560	Presumed infection, secondary
no change	≥ 7 days	≤ 1:1280	Not dengue
no change	< 7 days	≤ 1:1280	Uninterpretable
—	one specimen only	≤ 1:1280	Uninterpretable

<sup>1</sup> CLARKE, D. H. & CASALS, J. Techniques for haemagglutination and haemagglutination-inhibition with arthropod-borne viruses. *American journal of tropical medicine and hygiene*, 7: 561-573 (1958).

<sup>2</sup> These criteria were developed following extensive experience with virological and immunological studies on patients with dengue infections at the US Army Laboratory, Bangkok. Individual laboratories should establish baseline titres for the local population taken during a period of little or no dengue transmission. Titres more than twice the standard deviation of the geometric mean titre may be presumed to indicate recent secondary dengue infection. Alternatively, the sensitivity of the HI test system may be standardized in collaboration with a WHO Collaborating Centre (See Annex 6).





### Complement-fixation (CF) test

The CF test may also be used in serological diagnosis wherever facilities for the test exist. This test is less sensitive than the HI or neutralization test. Blood taken on filter-paper is unsuitable for the CF test because it is haemolysed.

The CF test is useful since only anti-dengue IgG fixes complement with dengue antigens. A four-fold rise in CF antibody where the interval between S1 and S2 is less than two weeks signifies a secondary seroresponse pattern.

### Neutralization tests

Although a number of neutralization tests have been described for dengue viruses, the most sensitive and specific method is the serum dilution, virus-constant, plaque-reduction test. Following primary dengue infections, relatively monotypic neutralizing antibodies are detected during early convalescence. Following secondary dengue infections, high-titred neutralizing antibody is produced against two to four dengue types. In some combinations of sequential infections, the highest neutralizing antibody titre in the convalescent serum is directed against the virus with which the patient was previously (*not* currently) infected, the so-called "original antigenic sin" phenomenon.

### Tests to detect IgM and IgG and dengue antibodies

Anti-dengue IgM is produced transiently during both primary and secondary dengue infections; detection of it in any single serum specimen indicates an active or recent infection. Anti-dengue IgG is also produced during both primary and secondary dengue infections but the quantity of anti-dengue IgG produced in secondary infections is much greater than in primary infections. Detection of anti-dengue IgM, and determination of the anti-dengue IgM to IgG ratio can be accomplished by (1) fractionation of the serum by density-gradient ultracentrifugation and testing the gradient fractions by HI, or (2) solid-phase "antibody-capture" ELISA. These are research techniques that may be very useful in some cases, for example fatal cases for which a definitive diagnosis could not otherwise be made.





## 5. Vector surveillance and control

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In most instances the most important, and often the only, vector of dengue haemorrhagic fever is *Aedes aegypti*. This vector should thus be the main target of surveillance and control activities wherever it occurs. Other vectors should be considered only where there is good evidence that they play an epidemiologically significant role in the transmission of the disease.

### Surveillance

A number of indices have been described and are currently used to monitor *A. aegypti* populations in terms of dengue transmission. The most significant of these indices are those related to the abundance of adult mosquitos expressed as either the landing rate or the indoor-resting density. Whenever adult collections cannot be made routinely to ensure an acceptable degree of monitoring, ovitraps can be used as a complementary method. Should the house index<sup>1</sup> and/or Breteau index<sup>2</sup> be used, *the definition of a house should be one unit of accommodation irrespective of the number of people therein.*

*A. aegypti* has a short flight range and a very large number of catching stations would be required to provide accurate monitoring of the areas at risk. As this cannot usually be done, the best alternative is to concentrate the monitoring on high-risk areas as determined by past experience and/or environmental conditions. Special attention should also be given to areas where control activities are carried out, in order to evaluate their effectiveness and develop remedial measures as appropriate.

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<sup>1</sup> Percentage of houses positive for larvae.

<sup>2</sup> Number of positive containers per 100 houses.





In a crowded area, many people living within the short flight range of the vector from its breeding source could be exposed to transmission even if the house index is low. Distances between houses may be of epidemiological significance, especially in areas with single-storey dwellings. In multi-storey dwellings the population per unit area could be higher than in slum areas. Thus survey data for single-storey and multi-storey dwellings should be kept separate.

Emergency control measures are based on insecticide applications and it is essential to monitor periodically the vector susceptibility to the insecticides most widely used for control operations, i.e., temephos (Abate) and malathion. Eggs can be sent to appropriate WHO Collaborating Centres for susceptibility testing when local facilities are not available.

In areas where *A. aegypti* is absent or very scarce and dengue outbreaks occur, a special effort should be made to identify the local vector(s) and to develop vector surveillance and control methods accordingly.

### Prevention and Long-term Control

Long-term control should be based on health education and community participation, supported by legislation and law enforcement wherever conditions permit. This should be supplemented by provision of an adequate water supply to the communities concerned. Larvicides should be considered as a complementary measure, and temephos 1% sand granules (10 g temephos per kg) can be applied at a target dose of 10 g of 1% sand granules to 100 litres of water, especially in high-risk localities before periods when outbreaks are expected.

The community should participate by undertaking the disposal of all unused objects that may collect water (e.g., old tyres, empty tins and bottles, broken jars, etc.) and by routinely changing the water in flower vases once a week. Whenever possible, water storage containers should be turned upside down before refilling with water.

Water jars and drums that cannot be disposed of should be adequately covered to prevent egg-laying by *A. aegypti*, or cleaned and scrubbed weekly. When this is not possible owing to their shape or size, *Aedes* larvae should be eliminated by transferring the water from one container to another through a cloth filter.

In certain areas, where vectors other than *A. aegypti* are present, coconut shells and husks can be buried or burned, tree holes can be filled with sand or cement, leaf axils can be punctured and the tops of bamboo fences altered to prevent accumulation of water and mosquito breeding. In coastal areas without a piped water supply, large water tanks with taps should be covered so as to allow rainwater to enter but exclude egg-laying mosquitos.





Since DHF is a permanent threat, health education should be provided regularly, beginning at schools and continuing throughout life, based on simple but accurate information and using all available media (school books, lectures, newspapers, radio, pamphlets, etc.). While health education should aim to cover the whole population, more specific efforts should be directed towards providing information for key components of the community, such as public health service staff and teachers. This health education should cover vector-borne diseases in general, with special emphasis on DHF wherever this constitutes a major problem.

### Emergency Control

To be effective, operations must begin when the first few cases are detected or when there are sound reasons to anticipate an outbreak.

The size of the area (or areas) to be treated should be determined through epidemiological and entomological information. If cases are scattered, space spraying with insecticides to kill adult mosquitos should be implemented as a minimum within a radius of 100 metres from houses in which there are cases.

Adulticidal treatments should be made at 7-10-day intervals if resources are available. Vehicle-mounted or portable ultra-low-volume (ULV) aerosol generators or mist blowers can be used to apply a suitable insecticide (e.g., technical malathion or fenitrothion) at rates above 0.5 litre per hectare.

It is suggested that moderate-sized cities have at least 1 vehicle-mounted aerosol generator, 5 mist blowers, 10 swing-fog machines, and 1000 litres of ULV insecticide in order to be prepared to carry out adulticidal operations rapidly over an area 20 kilometres square. When funds are limited, such equipment and insecticides can be stockpiled in one city for rapid transportation to other areas when required.

Priority areas for vector control are those with a concentration of cases and/or a high vector density. Special attention should be focused on areas where people congregate, e.g., hospitals and schools.

If necessary, ULV spraying by aircraft or helicopters can be explored.

Hospital rooms with DHF patients should be mosquito-proof.

### Training

Medical officers and personnel who see DHF cases should receive short training courses on vector biology and ecology so that they can





inform the community of the measures they should take to reduce vector breeding and biting.

Owing to the expense of maintaining special *Aedes* control teams, and in view of the shortage of trained manpower, national training courses on *Aedes* surveillance and control should be organized for health inspectors and related personnel to enable them to participate in control operations.





## 6. Epidemiological surveillance, contingency plans, control, and prevention

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### Factors Increasing the Risk of Outbreaks of Dengue Haemorrhagic Fever

The occurrence of DHF outbreaks is linked to the density of mosquito vectors and particularly to that of *Aedes aegypti*. The precise population density of *A. aegypti* that will sustain dengue virus epidemically or endemically in a community has not yet been determined. In many instances, a small number of actively biting, female mosquitos has infected an entire household. Virus transmission is enhanced by denser human populations. Urbanization in tropical countries has resulted in both the proliferation of *A. aegypti* and an increase in the number of susceptible human hosts.

In cities the movement of viraemic persons may be a more important means of transportation of the dengue viruses than is *A. aegypti*, which has a short flight range. Places where people congregate during the day may be important sites of dissemination of dengue viruses; schoolchildren bitten by infected mosquitos may take the virus home to other parts of the city. Dengue viruses may also spread in hospitals, if visitors, patients, and staff are bitten by infected *A. aegypti*.

Dengue viruses may be carried to smaller towns and rural areas from larger cities where the disease is epidemic or endemic. The factors affecting dengue transmission and maintenance in smaller towns are not well documented. Introductions over long distances have taken place in the Pacific and Caribbean regions repeatedly during the past 20 years.

In most places there seems to be a distinct seasonal pattern in DHF outbreaks. In subtropical regions, for example, where monsoon weather patterns prevail, it has been observed that, several months after the cessation of the rains, usually during cool dry weather, the DHF hospitalization rate declines. This decline in





dengue transmission may be related to a decrease in mosquito biting activity, a decrease in longevity of female mosquitos, or both, and possibly to a small decrease in the vector population. During these seasonal lows, virus transmission is most likely to occur only in areas of high transmission potential.

Typically, DHF cases are associated with secondary infections in childhood and with primary infections in infancy, although the DHF syndrome does also occasionally occur during primary infections in children. In Asia, DHF cases are seen in areas with a high density of *A. aegypti* and with more than one type of dengue virus, this combination of factors resulting in multiple infections in children, as evidenced by a typical pattern of secondary (anamnestic) serological response.

### Surveillance of Dengue Haemorrhagic Fever

The objective of a DHF surveillance programme is the early detection of outbreaks, thus permitting the prompt application of control measures. To accomplish this, all the important factors that favour an outbreak of the disease should be monitored. The monitoring of suspect cases, using the diagnostic criteria outlined above (page 11), as well as active reporting and epidemiological and entomological studies are required for satisfactory surveillance.

Surveillance is indicated in all dengue endemic areas as well as in "receptive areas", defined as areas where *A. aegypti* is known to be present. With the possibilities of modern air travel a viraemic dengue patient can be transported from an endemic to a receptive area within a single day. Thus, the introduction of any dengue virus into inhabited areas with sufficient populations of *A. aegypti* to facilitate transmission can and should be expected at any time.

Most dengue infections in young children are mild and difficult to distinguish from acute febrile diseases. Classical dengue fever is most commonly seen in adults, but in areas where dengue viruses are endemic, resident adults are generally immune.

It is important to understand that, as a general rule, a great amount of silent dengue infection has preceded and also accompanies DHF epidemics. It has been estimated that during outbreaks, between 150 and 200 mild or silent dengue infections occur for each case of DSS seen in hospital. An understanding of this phenomenon is essential to the planning of programmes to prevent and control DHF.

The following activities should all be included in a basic programme for DHF surveillance.





### Fever surveillance

In order to determine the presence of an epidemic of febrile illness a fever surveillance programme should be maintained; such a programme should include either (1) surveillance of fever cases, or (2) an etiological study of fevers of unknown origin.

1. For the surveillance of fever cases, sentinel clinics at strategic locations throughout the country should report on a weekly basis to the ministry of health: the number of patients seen, the number of patients with an oral temperature higher than 38°C, and an estimate of the number of people served. In this way abnormal increases in febrile illness can be detected. When these occur, an attempt should be made to determine their etiology.

2. For the etiological study of fevers of unknown origin, designated centres should undertake prospective hospital and laboratory studies of patients with fevers of unknown origin or suspected haemorrhagic fever, including examination of paired sera and attempts to isolate virus whenever possible.

### Recognition of cases

Standard criteria for clinical diagnosis and laboratory confirmation of DHF should be followed.

### Reporting of cases to national and international health authorities

Presumptive cases of DHF designated as being *with* or *without* shock should be reported to the appropriate national and international health authorities. An agency within the ministry of health should be designated to receive and compile this surveillance information. These data should be processed as rapidly as possible and frequent reports should be prepared for forwarding through the ministry of health to the individuals and institutions who provided the surveillance information, the appropriate WHO regional office, WHO headquarters in Geneva, and to all others who need to know. As a minimum, reports should include the numbers of DHF cases and of deaths by age and sex. Reports may be submitted in narrative or tabular form (Annex 7). The form should be signed by the medical officer responsible.

### Aedes surveillance

A country-wide survey should be made to establish the presence, population density, and seasonal prevalence of *Aedes* vectors and





their resistance to insecticides. WHO is always pleased to receive information arising from national *Aedes* surveys. Where there is a need for assistance for the conduct of such surveys, WHO is prepared to provide advice for the organization and guidance of such work.

### Serological surveillance

Serological surveillance may be used to detect silent dengue infections and the presence of specific dengue serotypes. Communities in which dengue infections are found would be "at risk" of DHF outbreaks if a different dengue virus type were introduced.

### Virological surveillance

The monitoring of dengue virus infections and of the occurrence of dengue virus types in dengue endemic areas should be instituted as soon as facilities and trained staff are available. At the outset, virological surveillance will consist of obtaining reports of virus isolations from patients and mosquitos wherever this information is available from arbovirus laboratories in the region. Whenever possible, original materials (viraemic serum or infected mosquito pools) as well as laboratory passaged strains should be preserved for future study. Isolation of viruses from DHF cases is essential. WHO should be contacted for advice concerning facilities for the storage of dengue viruses.

### Development of Epidemic Contingency Plans

Contingency planning should involve estimating the number of people at risk, determining the amount of equipment (including hospital beds and intensive care facilities), supplies, and personnel required for vector control and the management of patients (see Annex 7), and recording the present location of these resources.

### Necessary supplies for treating dengue haemorrhagic fever

As noted in Chapter 3, the fundamental therapeutic principle is rapid replacement of intravascular fluid by intravenous infusion. The following assumptions make it possible to estimate what supplies will be required:

- In the *worst* situation so far encountered (Cuba, 1981), the prevalence of seriously ill patients requiring hospitalization approached 1 case per 100 population.





- Hospitalized cases usually require some intravenous therapy with normal saline.
- About 20% of all hospitalized cases will require intravascular volume expanders such as Dextran 40, Plasmanate, albumin, or plasma.
- About 10% of all hospitalized cases will require whole blood.

Based on these assumptions, the following supplies are required per 10 000 population (100 cases of DHF):

100 cases of DHF	— 200–300 litres of normal saline
20 cases of DHF with hypovolaemia	— 20 litres of a volume expander in appropriate units
10 cases of DHF with haemorrhage	— at least 10 units of whole blood.

Most hospitals in urban areas have these quantities in hand. As the epidemic continues, replacement supplies should be procured in good time.

### Control of Outbreaks

In controlling outbreaks, two main operations have to be carried out simultaneously: (a) emergency mosquito control; and (b) treatment of patients in hospitals.

#### Emergency mosquito control

The following steps should be taken as soon as possible when an outbreak is suspected:

(a) The geographical area affected should be defined in order to determine the extent of the insecticide spraying operation required. For this purpose, presumptive cases of DHF should, if possible, be confirmed in the laboratory by serological examination of paired sera.

(b) An inventory should be made of the location, quantity, and availability of pesticides for use against adult mosquitos and of equipment such as ULV sprayers and trucks or aircraft that can be converted for use in spraying operations (see Annex 8).

Operations for emergency mosquito control should be carried out as described on page 32. The objective is to eliminate infected mosquitos and to break the transmission cycle by keeping mosquito populations at extremely low levels during the time necessary for viraemic subjects to recover. Complete control of an epidemic may not be feasible if all adult *A. aegypti* cannot be destroyed in the entire affected area. However, a sustained reduction of mosquito populations in selected areas will inevitably result in fewer cases.





## Organization of clinical care during epidemics

### *Organizational aspects*

An organizing or coordinating committee should be established to facilitate interdisciplinary and interagency communication and should consist of administrators, epidemiologists, clinicians, entomologists and virus laboratory workers; the responsibility for establishing this committee is usually vested in the ministry of health. The committee should: (1) design and distribute appropriate protocols for the diagnosis and treatment of DHF/DSS; (2) compile and distribute appropriate literature on DHF/DSS; (3) prepare and circulate informational material directed towards both health workers and the lay public; (4) plan and implement training programmes for health care workers and auxiliaries (e.g., hospital staff, medical students, nurses, and laboratory technicians); (5) assess the need for intravenous fluids, medications, blood products, intensive care equipment, teaching materials, and equipment for transporting patients; (6) supervise the use of supplies and the outcome of the clinical care programme (daily, if required); and (7) coordinate clinical research on DHF/DSS during the outbreak.

It may be necessary to provide additional beds for the acute care of patients, and some of those assigned to non-essential care, e.g., non-urgent surgery, may initially be taken over. When indicated, however, it may be necessary to set up hospitals in schools or other institutions, but this should be considered only if appropriate medical personnel and a laboratory capable of performing reliable haematocrits and platelet count determinations are available, since microhaematocrit determinations are essential in monitoring the need for therapy and its success. *It is recommended that all institutions providing care for DHF patients should have microhaematocrit equipment and microscopes for platelet estimation available.*

### *Triage*

During epidemics, outpatient and inpatient facilities may be overwhelmed and medical care staff can rapidly become exhausted. In these circumstances it is essential that only persons who genuinely require hospital care should be admitted (see flow chart in Annex 3). A fever and positive tourniquet test are sufficient for DHF to be suspected; when possible, a microhaematocrit and platelet count should be done in the outpatient department. Patients with thrombocytopenia and elevated haematocrit should be sent to a rehydration ward or, if circulatory failure is suspected, admitted to hospital. If a patient lives far away from the hospital and





accommodation nearby is not available, it may be necessary to admit him for observation. Patients or their parents should be carefully instructed that prompt return to hospital is necessary should restlessness, lethargy, acute pain, oliguria, or circumoral cyanosis be observed. Paramedical workers can carry out triage if they are properly instructed. Competent laboratory assistance is desirable but, without a laboratory, patients can be evaluated by physical examination—cool extremities, skin congestion, circumoral cyanosis, or a rapid pulse indicating that hospitalization is necessary. If possible, patients should be hospitalized for observation or warned that they should remain near the hospital until two days after fever subsides.

#### *Intensive care*

Patients with a similar degree of severity of illness should be grouped together. Those with shock require intensive 24-hour nursing and physician care. Paramedical workers or parents can assist by administering oral fluid therapy or by monitoring the rate of intravenous fluid administration and the general status of the patient.

### **Prevention of Dengue Haemorrhagic Fever**

Prevention of DHF outbreaks in endemic areas is based on long-term antimosquito control measures (see pages 31–32).

Research is being carried out to develop a live tetravalent vaccine against the four dengue virus serotypes. Although progress has been reported, it will be several years before an acceptable vaccine for mass use will be available.

### **Exchange of Information**

Rapid exchange of information is essential. Narrative epidemiological reports, results of clinical studies, dengue virus isolations by source and date, entomological studies and surveys for dengue vectors, and details of control measures planned or carried out, new developments in insecticides and spray equipment, and other pertinent information will be published in the dengue newsletters in the various WHO Regions. (The addresses of the editorial offices of these newsletters are listed in Annex 8.)





## 7. Primary health care

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DHF is often, though not exclusively, closely associated with poor environmental sanitation, inferior housing, and inadequate water supplies. Communities where such conditions prevail need to be told what steps they can take to prevent and control DHF. The diagnosis and management of DHF may pose a problem for primary health care workers, as may the control of outbreaks. The disease tends to spread from large cities to smaller ones and to villages infested by vector mosquitos, mainly *Aedes aegypti*. Transmission of the disease can be reduced by community participation in vector control. In addition, the case fatality rate of DHF can be considerably decreased if the appropriate replacement fluid therapy is given early in the course of the disease. Referral to a well-equipped hospital is not always possible, and health care workers should therefore be specially trained to cope with this situation. This applies particularly to rural areas.

### Recognition of Dengue Haemorrhagic Fever Cases

An outbreak of DHF should be suspected in the community when:

- Several children are found to be suffering from undiagnosed febrile diseases characterized by a high continuous fever of 2-7 days' duration. Suspicion of DHF is increased when such cases fail to respond to specific treatment for common diseases, e.g., malaria, meningitis, pneumonia, pharyngitis, etc.
- Unexplained deaths occur, with or without haemorrhage, within one week after the onset of an acute febrile illness.
- Fever patients have petechiae (red spots on the skin), bleeding from the nose or gums, haematemesis, or melaena.
- Fever patients remain ill despite a drop in temperature and the clinical situation deteriorates with the development of clammy skin, cold and sweaty extremities, drowsiness, and/or restlessness.





The first step towards community involvement in DHF control is for mothers to learn that seeking early medical care for their sick children may prevent a serious outcome. It is therefore important for mothers to be trained to recognize the early features of DHF so that they can take their children promptly to the health centre for adequate treatment. They should be taught that the symptoms suggestive of DHF are a high continuous fever (lasting 2–7 days) that may be accompanied by anorexia, nausea, vomiting, abdominal pain, and subsequent evidence of bleeding (persistent red spots in the skin or nose, or gum bleeding, coffee-ground vomit, or dark stools). In particular, they should be told to look for the early signs of shock—the patient remains ill despite a fall in temperature and develops a cold clammy skin, restlessness, or drowsiness.

### Management of Cases<sup>1</sup>

The flow charts in Annexes 3 and 4 may be helpful for the purposes of triage and treatment in primary health care centres.

High fever should be treated by sponging and/or appropriate use of paracetamol. Aspirin and other salicylates should not be given because they may lead to bleeding and cause gastric irritation and acidosis.

Oral rehydration must be attempted in the early stages of fever with the sugar and salt solution used for diarrhoeal diseases (see footnote on page 17), which should be given in repeated small quantities.

If there is any evidence of bleeding, the patient should be referred promptly to a hospital.

If the body temperature drops, the extremities become cold, and the patient becomes restless, prompt referral to a hospital or suitable health centre is necessary for intravenous fluid administration. If referral is not possible, oral rehydration should be continued until the child urinates and the skin becomes warm.

### Collection of Specimens for Laboratory Examination

Proof that the outbreak is caused by a dengue virus must be obtained as soon as possible after the first suspected cases have been recognized. As indicated on page 24, blood specimens should be collected on filter-paper discs or strips and sent with clinical data to a specialized laboratory. In addition, blood films should be made and sent to the nearest health centre laboratory to be stained for differential white-blood-cell and platelet estimation.

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<sup>1</sup> For more detailed information, see Chapter 3.





The recognition of cases and the collection of specimens can both be facilitated if a member of the community has been designated as a "health communicator" to provide liaison between the community and the health care group.

### Mosquito Control

The vectors of DHF breed in and around houses and, in principle, can be controlled by individual and community action. This approach should be adopted in extending vector control coverage to communities that do not routinely benefit from the activities of an organized vector control service.

The disease is transmitted by *Aedes* mosquitos. For practical purposes it may be assumed that the vector is *Aedes aegypti*, a mosquito that bites during the day, rests in houses, and lays eggs in artificial water containers. The appropriate control activities that communities and individuals can carry out are outlined on pages 31-32.

The duties of vector control personnel should include health education activities aimed at increasing community participation in the control of DHF vectors. They should collaborate in providing technical guidance in simple and understandable language to community leaders, primary health care workers, and others, such as schoolteachers, who often have day-to-day contact with the community. Special attention should be directed towards the instruction of members of communities, especially parents, in mosquito control methods.



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*Annex 1*

**LIST OF PARTICIPANTS\***

*Technical Advisory Group on Dengue Haemorrhagic Fever/  
Dengue Shock Syndrome, Kuala Lumpur, 30-31 August 1983*

- Y. H. Bang, Regional Entomologist, WHO Regional Office for South-East Asia, New Delhi, India
- N. Bhamarapravati, Director, WHO Collaborating Centre for Research on Immunopathology of DHF/DVD, Ramathibodi Hospital, Bangkok, Thailand
- D. S. Burke, Department of Virology, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand
- Y. Funahara, Department of Physiology, Kobe University School of Medicine, Kobe, Japan
- R. George, Consultant Paediatrician, General Hospital, Kuala Lumpur, Malaysia
- B. M. Gorman, WHO Collaborating Centre for Arbovirus Reference and Research, Queensland Institute of Medical Research, Brisbane, Australia
- S. B. Halstead, Department of Tropical Medicine and Medical Microbiology, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA
- S. Hotta, International Center for Medical Research, Kobe University School of Medicine, Kobe, Japan
- A. Igarashi, Professor and Chairman, Department of Virology, Institute for Tropical Medicine, Nagasaki University, Nagasaki, Japan
- R. Krzysko, Regional Adviser on Communicable Diseases, WHO Regional Office for South-East Asia, New Delhi, India
- S. K. Lam, Scientist, Virus Diseases, WHO, Geneva, Switzerland
- S. Nimmannitya, Senior Paediatrician, Children's Hospital, Bangkok, Thailand
- T. Pang, Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
- F. P. Pinheiro, Regional Adviser on Viral Diseases, WHO Regional Office for the Americas, Washington, DC, USA
- R. M. Scott, Chief, Virology, Walter Reed Army Institute of Research, NAMRU-3, Cairo, Egypt (*Rapporteur*)

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\* Unable to attend: Mi Mi Khin, Department of Medical Research, Ministry of Health, Rangoon, Burma.





- L. S. Self, Responsible Officer, Vector Biology and Control, WHO Regional Office for the Western Pacific, Manila, Philippines
- R. E. Shope, Yale Arbovirus Research Unit, WHO Collaborating Centre for Arbovirus Reference and Research, New Haven, CT, USA (*Chairman*)
- R. S. Songco, Director, Hospital of the Infant Jesus, Manila, Philippines
- H. Sumarma, Head, Division of Tropical Diseases, Department of Child Health, Medical School, University of Indonesia, Jakarta, Indonesia
- T. Umenai, Regional Adviser on Communicable Diseases, WHO Regional Office for the Western Pacific, Manila, Philippines
- T. Vitarana, Consultant Virologist, Medical Research Institute, Colombo, Sri Lanka



Annex 2

# DENGUE HAEMORRHAGIC FEVER RECORD SHEET

Name..... Age..... Sex..... Hospital No.....  
Race..... Weight.....  
Address .....

Day of illness	1	2	3	4	5	6	7	8	9	10	11	12	13
----------------	---	---	---	---	---	---	---	---	---	----	----	----	----

Month/Date  
(encircle date of  
hospitalization)

Max. temp. (°C/°F)

Pulse/BP

Tourniquet test

Petechiae

Purpura/ecchymosis

Epistaxis

Haematemesis/melaena

Other bleeding

Hepatomegaly (size)

Shock

Cold extremities

Cold, clammy sweating

Restlessness

Lethargy

Heart/lungs

Rash (describe)

Lymph nodes

Other signs

Haematocrit (%)

Platelets ( $\times 10^3$ )

WBC

Neutrophils (seq./stab.)

Lymphocytes/monocytes

Blood for virus/serology

Acute

Convalescent

Treatment

LR/PSS

Plasma

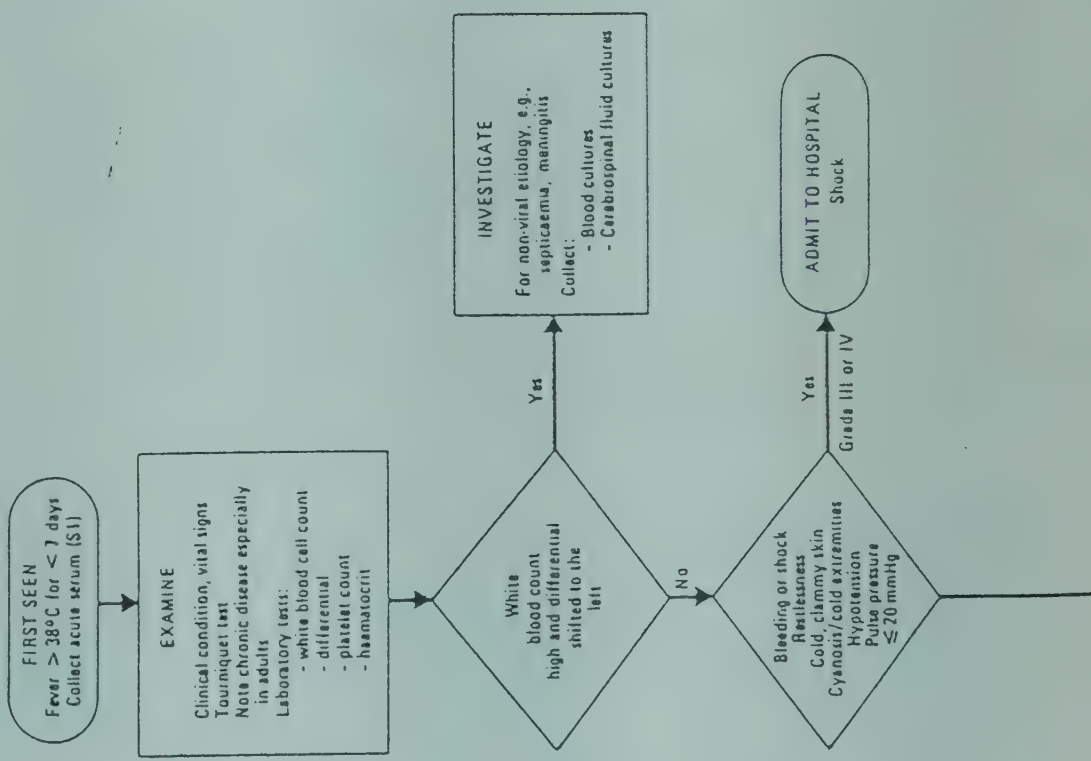
Blood

Other



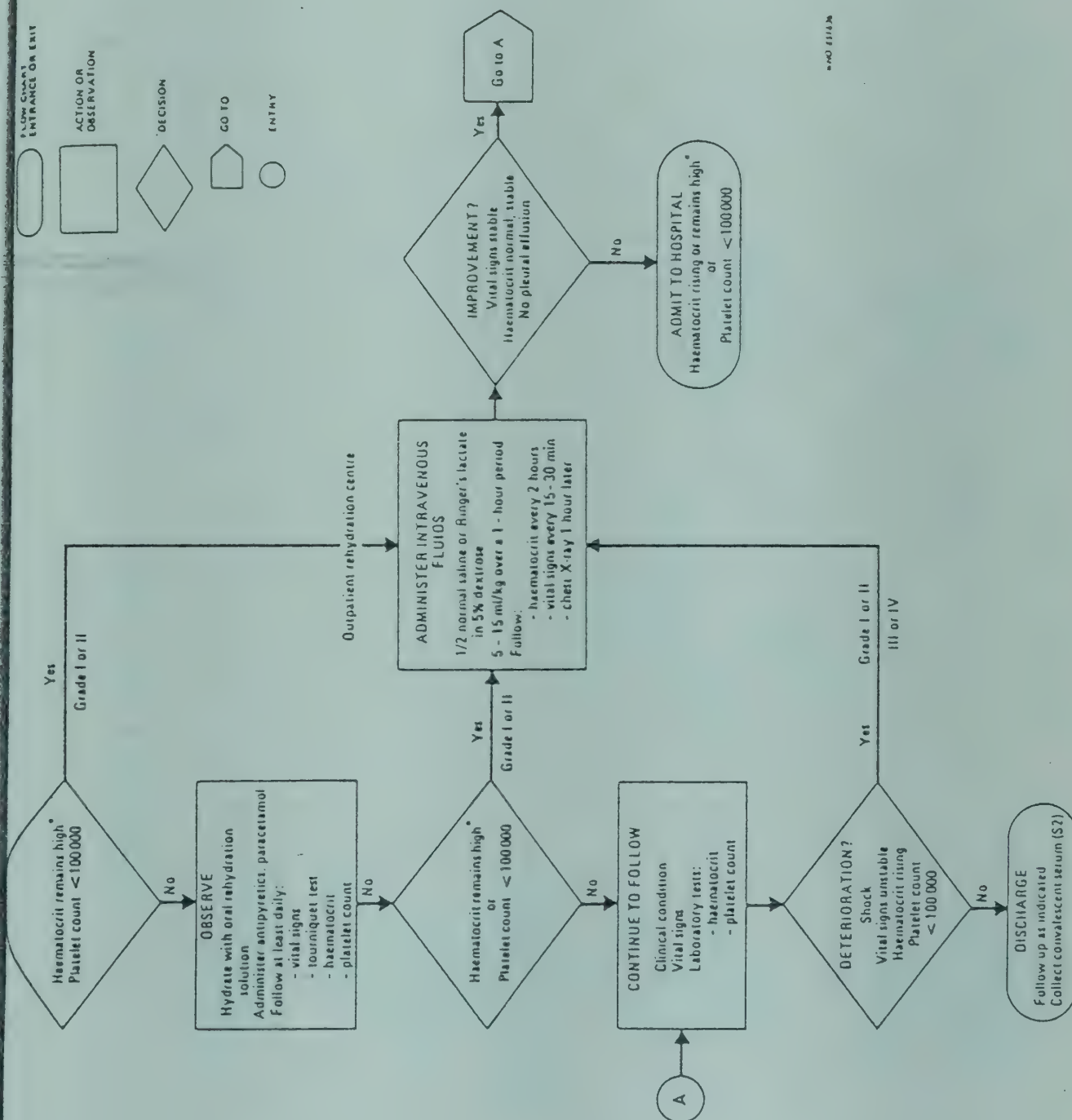


Annex 3  
OUTPATIENT FLOW CHART





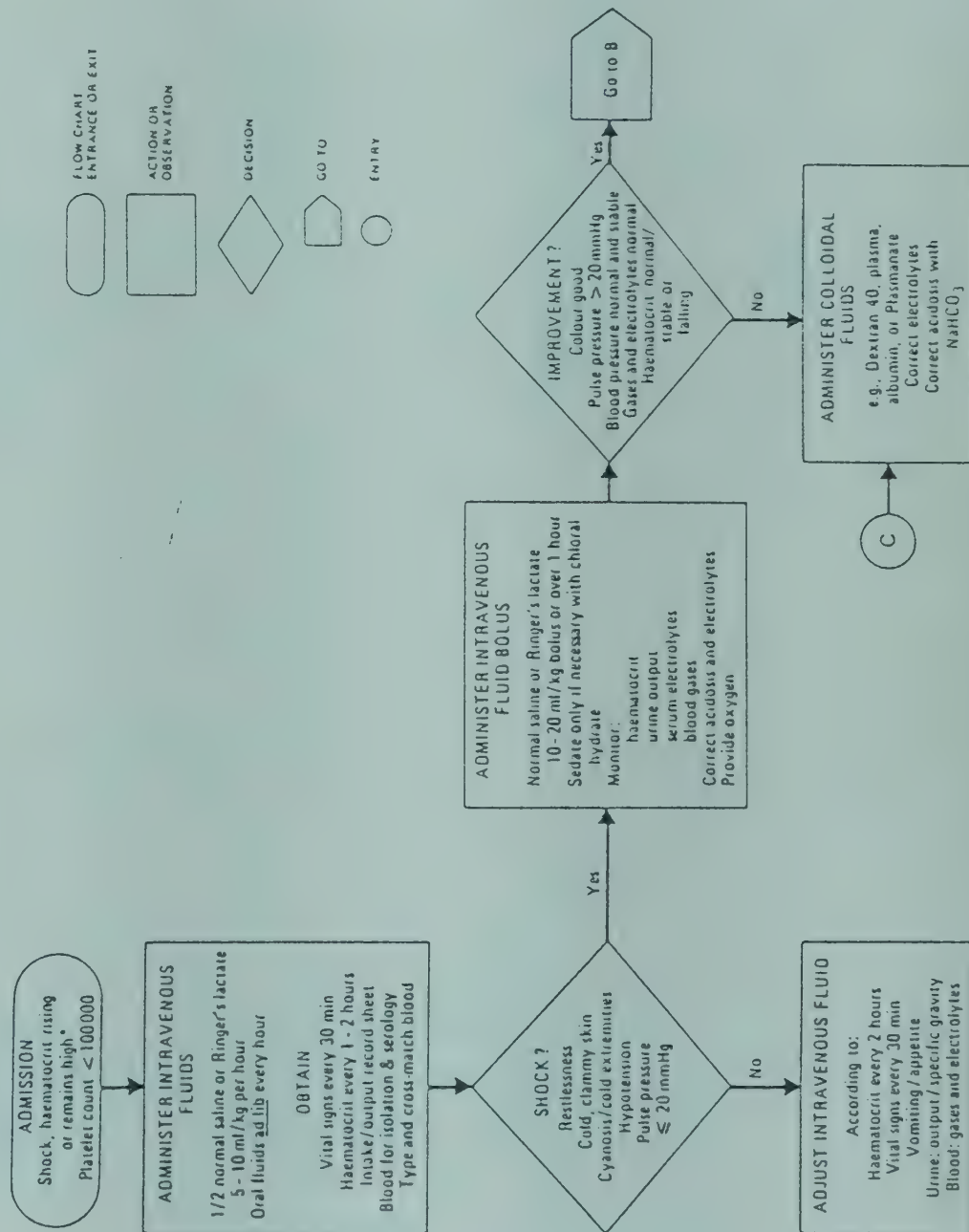






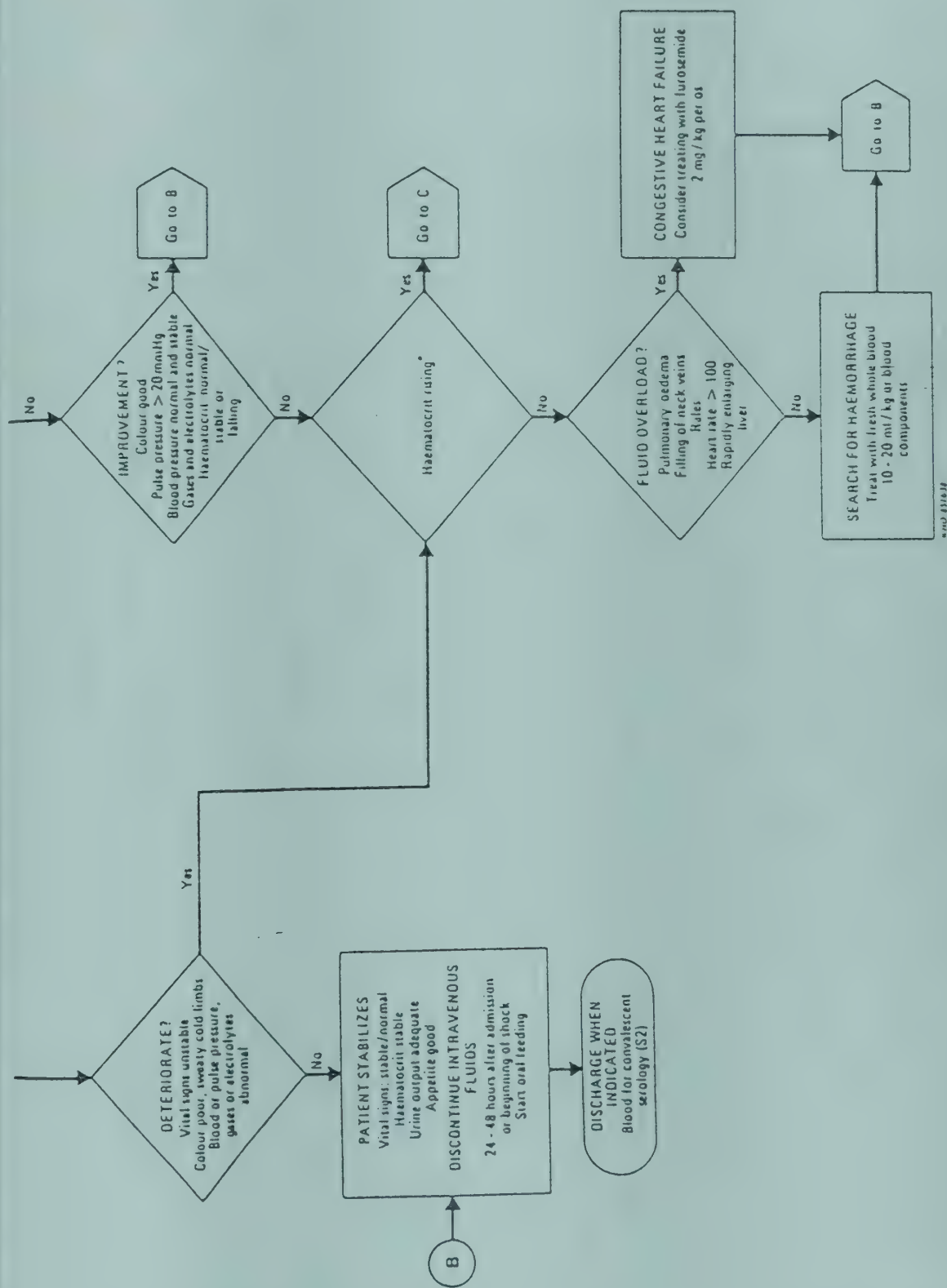
Annex 4

## HOSPITAL FLOW CHART













Annex 5  
ARBOVIRUS LABORATORY REQUEST FORM

For Laboratory Use

Name of patient \_\_\_\_\_ Hospital No. \_\_\_\_\_  
Address \_\_\_\_\_ Hospital \_\_\_\_\_  
Age \_\_\_\_\_ Sex \_\_\_\_\_ Physician \_\_\_\_\_  
Date of admission \_\_\_\_\_ Admission complaint \_\_\_\_\_  
Date of onset \_\_\_\_\_

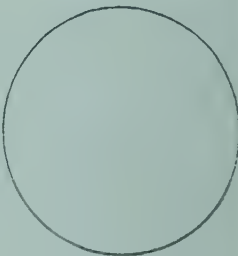
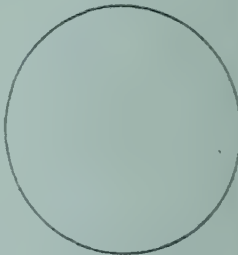
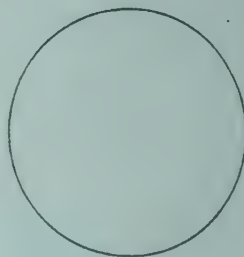
Clinical findings: 1. Fever \_\_\_\_\_ °C or °F (max). Duration \_\_\_\_\_ days  
2. Tourniquet test \_\_\_\_\_ Petechiae \_\_\_\_\_ Epistaxis \_\_\_\_\_  
Haematemesis/melaena \_\_\_\_\_ Other bleedings (describe) \_\_\_\_\_  
3. Hepatomegaly \_\_\_\_\_ (cm at RCM). Tenderness \_\_\_\_\_  
4. Shock \_\_\_\_\_ B.P. \_\_\_\_\_ mmHg Pulse \_\_\_\_\_/min  
Restlessness/Lethargy \_\_\_\_\_ Coldness of extremities/body \_\_\_\_\_

Clinical laboratory findings:

Platelets (  $\times 10^3$  ) \_\_\_\_\_ /mm<sup>3</sup> (on \_\_\_\_\_ day of illness).  
Haematocrit (%) \_\_\_\_\_ (max) \_\_\_\_\_ (min)

Blood specimens

(Acute) Hospital admission Date \_\_\_\_\_  
Hospital discharge Date \_\_\_\_\_  
Convalescent Date \_\_\_\_\_



Instructions: Fill out entire form and clinical findings in duplicate. Fill filter-paper discs completely so that reverse side is saturated and clip them on the form. Obtain admission and discharge specimens from all patients. If patient does not return for convalescent sample, mail promptly.



Annex 5 (continued)  
ARBOVIRUS LABORATORY REPORTING FORM

To: Physician \_\_\_\_\_ Date \_\_\_\_\_  
Address \_\_\_\_\_ Hospital \_\_\_\_\_ Patient \_\_\_\_\_ Hospital No. \_\_\_\_\_

Clinical findings: 1. Fever \_\_\_\_\_ °C or °F (max). Duration \_\_\_\_\_ days  
2. Tourniquet test \_\_\_\_\_ Petechiae \_\_\_\_\_ Epistaxis \_\_\_\_\_  
Haematemesis/melaena \_\_\_\_\_ Other bleedings (describe) \_\_\_\_\_  
3. Hepatomegaly \_\_\_\_\_ (cm at RCM). Tenderness \_\_\_\_\_  
4. Shock \_\_\_\_\_ B.P. \_\_\_\_\_ mmHg Pulse \_\_\_\_\_/min.  
Restlessness/Lethargy \_\_\_\_\_ Coldness of extremities/body \_\_\_\_\_

Clinical laboratory findings:  
Platelets (  $\times 10^3$  ) \_\_\_\_\_ /mm<sup>3</sup> (on \_\_\_\_\_ day of illness)  
Haematocrit ( % ) \_\_\_\_\_ (max) \_\_\_\_\_ (min) \_\_\_\_\_

FOR LABORATORY USE ONLY	
Results	HI titres
Dates of specimens	
Interpretation	





*Annex 6*

**WHO COLLABORATING CENTRES  
FOR ARBOVIRUS REFERENCE  
AND RESEARCH**

- Queensland Institute of Medical Research, Bramston Terrace,  
Brisbane, Queensland 4006, Australia
- Instituto Evandro Chagas, Divisao de Virologia, C.P. 621, 66000  
Belém, PA, Brazil
- Institute of Virology, Slovak Academy of Sciences, Mlynska dolina,  
809 39 Bratislava 9, Czechoslovakia
- Unité d'Ecologie Virale, Institut Pasteur, 25 rue du Docteur Roux,  
Paris 75724—Cedex 15, France
- National Institute of Virology, 20-A Dr Ambedkar Road, P.O. Box  
11, Pune 411 001, India
- Department of Virology and Rickettsiology, National Institute of  
Health, 10-35 Kamiosaki, 2-Chome, Shinagawa-ku, Tokyo 141,  
Japan
- Department of Medical Microbiology, Faculty of Medicine,  
University of Malaya, Kuala Lumpur, Malaysia
- Institut Pasteur, 36 avenue Pasteur, Boite postale 220, Dakar,  
Senegal
- Arbovirology Department, Uganda Virus Research Institute, P.O.  
Box 49, Entebbe, Uganda
- Institute of Poliomyelitis and Virus Encephalitides, P.O. Institute of  
Poliomyelitis, Moscow Oblast 142 782, Union of Soviet Socialist  
Republics
- Vector-Borne Diseases Division, Center for Infectious Diseases,  
Centers for Disease Control, P.O. Box 2087, Fort Collins,  
Colorado 80522, USA
- Yale Arbovirus Research Unit, Department of Epidemiology and  
Public Health, Yale University School of Medicine, 60 College  
Street, New Haven, Connecticut 06510, USA





## Annex 7

# DENGUE HAEMORRHAGIC FEVER CASE-REPORTING FORM

Covering period from ..... to .....

Country/district/town .....

[illegible]

Date ..... Signature .....



## *Annex 8*

# CHECK-LIST FOR MANAGEMENT OF DENGUE HAEMORRHAGIC FEVER OUTBREAKS, SURVEILLANCE, AND REPORTING

### Patient management

- hospital beds and intensive care facilities
- intravenous fluids
  - physiological saline
  - Ringer's lactate
  - 1/6 mol/litre sodium bicarbonate
- colloidal fluids (one or more of the following)
  - fresh frozen plasma
  - plasma
  - plasma protein fraction, human 5% (Plasmanate)
  - Dextran-40, medium relative molecular mass
  - blood products
  - whole blood
  - platelet concentrate
- oral rehydration solution (see page 17)
- analgesics
  - paracetamol
- sedatives
  - chloral hydrate
- diuretics
  - furosemide
- cardiotonics
  - digoxin
- oxygen and delivery system
- paediatric blood pressure cuff.

### Laboratory

- microhaematocrit centrifuge, capillary tubes, and reader
- platelet counting equipment—phase-contrast microscope, counting chamber and pipettes, or ordinary microscope for platelet examination
- microscope slides





- blood-drawing equipment, tubes, pipettes, EDTA tubes, heparin tubes, citrate tubes, plain tubes
- serum or plasma storage
  - 20°C freezer for serological specimens
  - 70°C freezer or liquid nitrogen for virus isolation specimens
- specimen shipping equipment (consult local or regional diagnostic virology laboratory for suggestions)
- clinical biochemistry, haematology and pathology laboratory facilities
- for assistance with virological laboratory work
  - San Juan Laboratories,  
Dengue Branch, Division of  
Vector-Borne Viral Diseases,  
Center for Infectious Diseases,  
Centers for Disease Control (CDC),  
GPO Box 4532,  
San Juan, Puerto Rico 00936
  - Chief, Department of Virus Diseases,  
Walter Reed Army Institute of  
Research (WRAIR),  
Washington, DC 20012,  
USA
  - and WHO Collaborating Centres for  
Arbovirus Reference and Research (see  
Annex 6).

### Control

- pesticides for adult mosquitos
  - ULV formulation of malathion
  - ULV formulation of fenitrothion
- spray equipment
  - vehicle mounted ultra-low-volume aerosol generator or thermal fogger
  - mist blower, back-pack with ULV nozzle
  - swing-fog machine
- mosquito screening for hospitals
- larvicides
  - Abate (temephos) 1% sand granules for potable water (another larvicide may be used in containers not holding potable water)
- source-reduction or community clean-up campaign
- ovitrap (jars and paddles)
- teaching and information material
  - posters, pamphlets, films, slide cassettes, video tapes, articles for newspapers, radio and television, etc.





**Surveillance**

- case-reporting forms (Annex 7)
- arbovirus laboratory diagnosis and reporting forms (Annex 5)
- names, addresses, telephone numbers:
  - local or national epidemiologist
  - local or national public health officer
  - local or national virology laboratory supervisor
  - local or national vector control supervisor
- names and addresses of appropriate national and international public health authorities
- addresses of offices/newsletters for case- or outbreak-reporting

Editor, Weekly Epidemiological Record  
World Health Organization  
1211 Geneva 27  
Switzerland

Editor, Dengue Newsletter  
WHO Regional Office for South-East Asia  
World Health House,  
New Delhi 110002,  
India

Editor, Epidemiological Bulletin,  
Epidemiology Coordination,  
Pan American Health Organization,  
525 23rd Street, N.W.,  
Washington, DC, 20037,  
USA

Editor, Dengue Surveillance Summary,  
San Juan Laboratories,  
Dengue Branch, Division of Vector-Borne Viral Diseases  
Center for Infectious Diseases,  
Centers for Disease Control (CDC),  
GPO Box 4532,  
San Juan, Puerto Rico 00936



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Issued to field  
Bangalore station on 21/10/93

Dengue haemorrhagic fever is an increasing public health problem in most tropical areas in South-East Asia and the Western Pacific, and has recently been spreading in some parts of the American tropics, where in 1981 a very serious epidemic occurred in Cuba.

Drawing on experience from all these areas, this book provides valuable guidance to health staff at all levels who are called upon to care for patients or who are concerned with routine surveillance or the control of outbreaks. The final chapter indicates how primary health care workers can make important contributions by learning to recognize possible cases of dengue haemorrhagic fever at an early stage and by helping to reduce the numbers of the mosquitos that transmit the dengue virus.

NATIONAL INSTITUTE OF VIROLOGY  
BANGALORE UNIT  
VICTORIA HOSPITAL  
BANGALORE-560 002

Price: Sw.fr.13.—







need to return to India".

The Pena memorandum goes

is not a good thing. The CS should not be so childish."

# CET counselling from tomorrow

Education Correspondent

BANGALORE: Counselling for admission to professional colleges in Karnataka by the Common Entrance Test (CET) cell will commence on Saturday.

Candidates claiming seats under the physically handicapped quota will be counselled on the first day. The candidates have to produce a medical certificate issued by a com-

petent doctor as specified by the cell.

The students will have to appear before a committee comprising the Special Officer, CET cell, besides two specialists nominated by the director of medical education. There will be no counselling on July 26.

On July 27, students who have participated in state, national and international sports events and won medals will be counselled. Stu-

dents from Karnataka who participated in Republic Day camps and events in New Delhi and who have won the best cadet award will be counselled on July 28.

Counselling for Karnataka students (medical and dental), who do not fall under these categories, will begin on July 30 and ranks 1 to 1,000 would be counselled on that day.

## Dengue fever grips Bangalore

Sriranjan Chaudhuri

BANGALORE: Dengue fever, which created a scare when it broke out in Devanahalli on the outskirts of Bangalore a little more than a year ago, has been doing the rounds of the city on a regular basis again. While most doctors say that the situation is not yet alarming, others suggest the incidence of unexplained fevers could be a matter of concern.

Doctors are, however, happy and relieved that the dengue haemorrhagic fever that can even result in deaths has still not made serious inroads into the city.

For about a month now, Bangaloreans have been reeling under a 'virus' attack with complaints of fever, severe back and body pains and coughs which simply refuse to go away. It is while treating these that some cases of dengue (which is spread by mosquitoes) have come to light.

According to Victoria Hospital superintendent Dr S. Chikka Moga: "Dengue has been there for some time now and is not really new. We keep seeing cases regularly, but fortunately they are not yet of the haemorrhagic variety."

He added that in all cases of unexplained fevers, blood samples were sent for tests and dengue showed up through these.

Private hospitals have also been seeing cases regularly. Says Dr

### SYMPTOMS OF THE FEVER

Dengue fever or Break Bone Fever is also a viral fever. The best and simplest way to distinguish it from the others is by doing a blood test called the dengue serology test.

The symptoms according to experts are:

- Fever
- Extreme body ache especially in the back and limbs.
- Saddle-type fever — appears for about 2-3 days and then disappears only to make a reappearance after another 4-5 days.
- Exhaustion and tiredness.
- Reddish patches on the extremities.
- Bleeding through the nose and spots appearing on the limbs are a pointer to serious dengue haemorrhagic fever.

Dengue is transmitted by the *Aedes aegypti* mosquito, which breeds in water that has been stored over a period of time. So badly designed overhead tanks or air coolers/air-conditioners could cause a problem.

S.V. Chowti, consulting physician at Mallya Hospital: "We are currently treating six dengue cases and had another eight last month." He added that in several cases where the patient came in with complaints of fever, white blood cell (WBC) counts were just 2,100-2,400 when compared to the 4,000-11,000 that are normal. Some of these cases had to be put under 'barrier nursing' or put in isolation. Only serious dengue fever cases with low WBC counts need hospitalisation. Dengue haemorrhagic fever cases are kept under observation in hospitals.

The Manipal Diagnostic Services (MDS), which routinely does checks on blood samples

from patients within the city and rural areas, has also seen about 15 cases recently. "Another 12 cases are suspect and need a second test for confirmation," says Dr Satish Amarnath of MDS.

Doctors say the silver lining is that there is no clustering yet of the cases that have been reported. In June and this month, cases had been reported from R.T. Nagar, Jayanagar, Sampangiramanagar and K.R. Puram.

However, experts point out that this is no time for complacency. They suggest that being two different manifestations of the same disease, the presence of one may indicate that the other is lurking around.

## Karnataka, A MPs clash in RS over Alm

Sabina Inderjit

NEW DELHI: After Cau was the turn of the Kris make waves in the Rajya Sa Thursday with members from nataka and Andhra Pradesh ing to set the record straight

In a special mention on matti dam, R R Ramchand the TDP said Andhra P farmers had been affected the non-implementation Bachawat award. Karnata said, was not cooperating.

His party colleague Narayanswamy said that concerned must abide by bunal verdict and wanted tre to initiate steps to end pute.

However, H Hanuma (Cong) from Karnataka sa the state government had r lated any clause of the awa Bommai (Janata Dal) sug that a meeting of the chief ters of Karnataka, Andhra and Maharashtra be conve settle the Krishna issue.

"We have accepted the a he said. And, H.K. Javare (JD) also accused Andhra of creating hurdles in the ra the height of the Almatti Da

## BJP decision on Speakership to

The Times of India News Ser

NEW DELHI: With bare more days to go before this ment session ends, the B government has still to n candidate for the post o Sabha Deputy Speaker.

Prime Minister Atal Beh payee is now convening a r of the BJP and its allies o to discuss the issue, part since Lok Sabha Speaker Balayogi has asked the gove to decide on the deputy sp post before this session end

Differences between ti and its allies over choice of didate have delayed a dec far.

## Karnataka govt finds 36,000 jobs redundant

Employees in these posts will be shifted to other useful ones

Srinivasa Prasad

BANGALORE: The Karnataka government has tentatively identified as many as 36,000 posts in its service as "redundant" and is likely to do away with them.

The state government's department of personnel and administrative reforms (DPAR) has identified these redundant posts on the basis of certain guidelines laid down by a cabinet sub-committee headed by Deputy Chief Minister Siddaramaiah



dundant posts so far identified account than one per cent of the total number of government employees.

A senior minister, who is on the sub-tee, said: "The government blindly set th of five per cent and it does not mean stick to it. The percentage of redundant ees can be more or less than five per cent

The government also has to decide on do with the redundant staff. "We will o not retrench them and send them streets," said another senior minister. " does the redundant employees in oth











